IMPROVING SYNTHETIC EFFICIENCY THROUGH C—H ACTIVATION

BY

DUSTIN JOSEPH COVELL

DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Chemistry
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2011

Urbana, Illinois

Doctoral Committee:

Professor M. Christina White, Chair
Professor Scott E. Denmark
Professor Paul J. Hergenrother
Professor Martin Hw. Gruebele

ABSTRACT

Selective C—H activation methods provide a complementary approach for synthesizing complex small molecules, which traditionally are constructed by chemists using C—C bond forming reactions to join preoxidized fragments. Furthermore, the strategic application of C—H activation reactions has considerable potential for improving the overall efficiency of synthetic endeavors by introducing functionality directly into preassembled hydrocarbon frameworks, mitigating the effect of having to carry reactive functionality throughout a reaction sequence. With this goal in mind, this work describes a series of projects that develop and implement novel C—H oxidation reactions and strategies.

Firstly, a mild and efficient oxidation strategy for the preparation of chiral polyols is presented and validated through an enantioselective synthesis of differentially protected L-galactose. This synthesis is enabled by the development of a highly regio- and stereoselective linear allylic C—H oxidation reaction that generates 4-methoxybenzoate derivatives of chiral (*E*)-2-butene-1,4-diols directly from readily available chiral homoallylic alcohols and carboxylic acids.

Secondly, this work details the discovery of a heterobimetallic Pd^{II}bis-sulfoxide/(Salen)$Cr^{III}F$ catalyst system for asymmetric allylic C—H oxidation of terminal olefins. Evidence is provided that supports a model in which a chiral Lewis acid co-catalyst interacts with an organometallic intermediate and influences the stereochemical course of the catalytic process. Additionally, this work establishes that the asymmetric branched allylic oxidation reaction can be combined with other enantioselective transformations to afford enantiopure, polyoxygenated allylic alcohols rapidly and in good yields.

Thirdly, this work outlines the development of a novel catalytic palladium(II)-based method for the conversion of ketones, ketoesters, and aldehydes directly to their unsaturated homologs, without the need for prior activation of the carbonyl. Importantly, this reaction shows good to excellent reactivity and unprecedented selectivities for a number of substrates with a diverse array of functional groups. Preliminary mechanistic studies suggest the reaction proceeds through a Pd-enolate intermediate that undergoes successive β-hydride elimination to give the desired unsaturated carbonyl compounds, and that the acid additive is a key promoter of the reaction.

ACKNOWLEDGMENTS

My journey from cradle to Ph.D has been guided and shaped by more individuals than I can remember, but I'd like to briefly thank several of the most influential. Firstly, my advisor, Maria Christina White, whom welcomed me into her lab and pushed me from day one to be better. I have always taken great pride in my personal desire to improve, but thanks to Christina I have achieved greater heights than I ever imagined. Additionally, getting to experience her growth as an advisor and professor over these past six years has taught me much that will make my own quest into academia that much easier.

Secondly, I must thank my committee of Professor Scott E. Denmark, Professor Paul J. Hergenrother, and Professor Martin Hw. Gruebele for their overwhelming positivity and encouragement throughout my Ph.D career. I have heard many horror stories of intense and even brutal meetings with Ph.D committees; however this group has been tough but fair from the very beginning. I was always treated and talked to as if I were a colleague, and time was always taken to nurture my growth as both an professional and an individual. I cannot thank them enough for their guidance. In the same vain, my development as an educator, something about which I am deeply passionate, was aided significantly by Prof. Wilfred van der Donk, Dr. Lynne Miller, Prof. Jeff Moore, Prof. Robert Coates, and Prof. M. Christina White. I was both a teacher's assistant and a student of how one teaches at the highest level with each of them, and my future students thank you for your guidance.

Not only at the University of Illinois was I blessed with excellent professors, but also at my undergraduate institution, Macalester College. Though many faculty members significantly altered my worldview and helped me choose a course which I could not be happier to be on, one individual, Prof. Rebecca Hoye, went far above and beyond the call of duty as both an instructor and mentor. Her tremendous knowledge and patience serve as the model I try to emulate to this day. Importantly, she also showed me what it was to truly love what you do, and how to have fun while doing it. I have turned to her for advice and an encouraging word during graduate school and she has always made the time to provide both, even many years after I last walked through her labs. Prof. Hoye is truly a hero to me. Thank you.

The White group is a special beast and those who have shared this near familial bond with me are the only reason I was able to get through the day-to-day of graduate school. Ken (Big K) and Mark

(Ptarmigan) were the original members, who set a high bar to say the least. Ken was the *de facto* lab manager when I joined the group and his guidance in organometallics was essential to my landing on my feet in the lab. His importance to the lab was best demonstrated by our honoring him with an impromptu festival (Ken-fest 2K10) when he came back for a visit. Mark, while unnecessarily wary of Midwest tunnels, taught me how to be fearless in experimentation. His ability to design catalysts and tease out their reactivity is truly inspiring. Mark and I had many discussions, both of chemistry and life, which will not soon be forgotten

My classmates in the White group are two individuals who deserve special discussion. Firstly, Dr. Jared (Wildebeest) Delcamp was simultaneously my best friend and my lab mentor. His tenacity and passion are rivaled only by his sense of humor and his smile. The times I spent getting to know him, and eventually his wife Leah, are amongst my happiest in the last few years. Though it remains to be seen if the world will fully appreciate the duo of Jared and Dustin, the partnership of Simkin 42 and Eccos has already left its mark upon many an ego in the realm of Xbox live. Secondly, my South African friend Nicolaas (Nico) Vermeulen is an individual like no other. I was lucky enough to work with him on my first project, and to debate with him ever since. He is a man who is hard to put your finger on, but he has always been there when I have really needed someone, professionally or personally. It is my sincere wish that I get to sail on his pirate ship someday.

Many other White group members have left there mark on me and I only wish that I had learned more from this amazing collection before leaving. Eric (Klondike Bear) Stang is easily the best synthetic chemist I have known. His instinct for chemical reactivity has helped me many times, and his laughter is infectious. Sean Reed taught me the value of running the proper controls and his fascination with pure science has been a constant reinvigorating force. Andrew (Roo) Young has a mind that easily sees through the subtleties of catalytic reaction mechanism, and my discussions with him have been essential for my own research. Grant Rice and I spent more time together than most couples for three years. An odd couple on the surface, and an odd couple at the core…I'll miss you fanboy. Marinus (Bigi) is a model of practicality and efficiency in lab, generating more interesting, well thought out ideas than almost anyone else. His occasional smile is even more impressive. Paul Gormisky is wise beyond his years, generous, and a truly nice guy. I look forward to his meteoric rise and will do everything I can to be sure our paths

cross again. Iulia (Qlaw) Strambeanu has a heart made of pure gold, but mixed with her kindness is a tenacity that should not be underestimated. I look forward to our next “girl talk”. On joining the White lab, Shauna Paradine became the best student we had from Southwest Michigan…I expect big things. Tommy (Tom Tom) Osberger not only reignited my passion for chemistry when he joined the lab, he shared some of his dance moves too. I hate to go, but I know he’ll love to watch me leave. Greg (G-snake) Snapper introduced me to Dubstep and constantly reminded me how much older than him I am…kids these days. The pleasure was all mine. Alex Brucks, Anthony Mazzotti, Chao Jiang, Tobias Thaler, Tzlil Perahia, ClaireKnezevic, and Chris Taylor all briefly spent time in the lab, and I enjoyed every second of their company.

My extended family has been incredible in helping me through life and graduate school. Never once did they doubt my abilities or question my decision to shoot for the stars. They have constantly encouraged me when I tried and caught and propped me up when I have fallen. They have shared in my joy, exalted my successes, and cast away all my doubts. I am truly blessed, and I love each of you very much.

I have met too many friends at UIUC and beyond who supported me through this and other challenging segments of my life to thank individually, but know that your kindness to me will never be forgotten. I love each and every one of you, and my greatest wish is to see you succeed and be happy in your own lives.

Thanks beyond words go to my mother, Jeanie Sluder, my father, Danny Covell, my step-father, Dave Sluder, and my sister, Amanda Covell. The core of who I am developed mainly because of these four special individuals. My mother taught me passion and persistence. She showed me that ones heart can be their greatest asset, and that “feeling” things is as important as “knowing” them. My father taught me patience and observation, two skills essential to any scientist. Equally important, he taught me how to have fun, and that laughter, not anger, was the best way to resolve conflict. My step-dad treated me like an adult from our first meeting. His willingness to give me significant responsibility and hold me to the very highest standard gave me the confidence to be the man I am today. My little sister is the smartest, kindest, most stubborn, big hearted, amazing, and creative person I know. Her personal journey to become a nurse has been truly inspirational. I love you guys with all my heart. Thanks for helping me become me.

TABLE OF CONTENTS

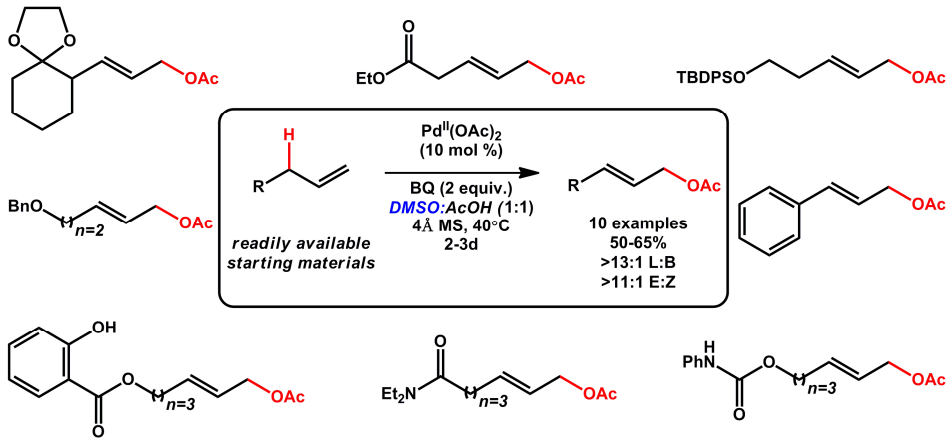
Chapter 1

Polyol Synthesis via Hydrocarbon Oxidation: De Novo Synthesis of L-Galactose[1]

1.1 Introduction

The strategic application of C—H oxidation reactions has shown significant potential for improving the overall efficiency of complex molecule synthesis by introducing oxygen and nitrogen functionality directly into preassembled hydrocarbon frameworks.[2,3,4] Selective C—H activation methods provide a complementary approach to the traditional strategy of C—C bond forming reactions between preoxidized fragments. An important subset of these reactions, catalytic allylic oxidations, have been known for over 40 years,[5g,h] however, most are limited by low conversions and/or lack of substrate generality due to poor functional group tolerance. Mild allylic oxidation methods using palladium(II) salts in acetic acid (AcOH)[5a-f] are available for transforming internal olefins into regioisomeric mixtures of allylic acetates. These reactions are believed to proceed via substitution of π-allyl-Pd intermediates generated through allylic C—H cleavage.[5a-f,6a,b] For reasons that are not fully understood, under these same conditions α-olefins predominantly undergo Wacker oxidation to yield mixtures of vinyl acetates and methyl ketone.[5e, 6c,d]

Figure 1.1. Catalytic linear allylic oxidation of α-olefins with $Pd(OAc)_2$/DMSO/BQ

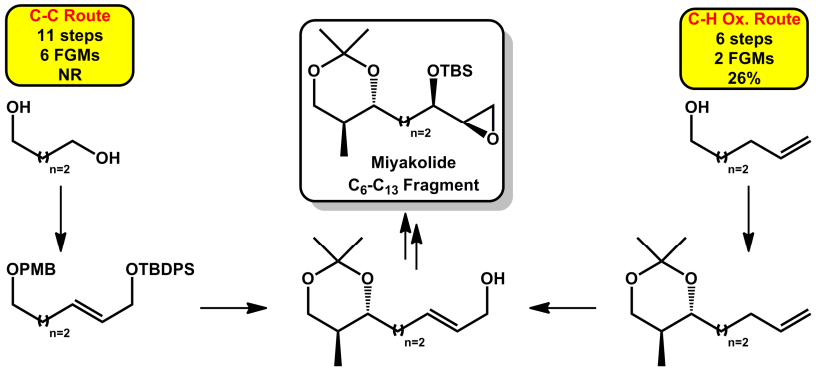


In 2004, White and Chen discovered that addition of dimethyl sulfoxide (DMSO) to a $Pd(OAc)_2$/benzoquinone(BQ)/AcOH catalyst system resulted in a C—H oxidation method for converting a variety of α-olefin substrates to linear (*E*)-allylic acetates with high regio- and stereoselectivities in moderate yields (Figure 1.1). This was the first report of DMSO acting as a ligand to significantly alter both the reaction pathway selectivity

and regioselectivity in a Pd(II)-catalyzed oxidation,[3a] though DMSO had been widely used in Pd(II)-mediated oxidation systems to promote reoxidation of Pd(0) with O_2.[7]

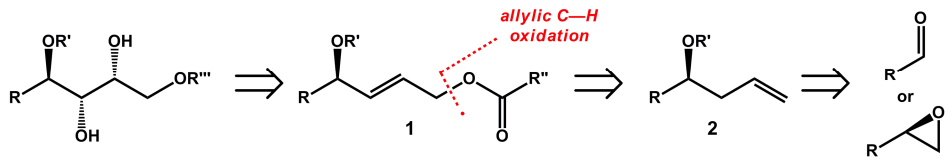
In 2005, White and Fraunhoffer reported a direct comparison of the C—H oxidation approach to the traditional joining of preoxidized fragments via C—C bond-forming methods for the production of (*E*)-linear allylic acetates.[8] They showed that carrying oxygenated functionality through a synthesis often necessitates the use of functional group manipulations (FGMs) (e.g. subsequent reactions to adjust oxidation state, alcohol protection-deprotection sequences, etc.) and that this negatively affects synthetic efficiency (*i.e.* total yield and number of synthetic steps). Alternatively, direct oxidative functionalization of hydrocarbon units late in a synthetic sequence proceeded with fewer FGMs, resulting in shorter syntheses and increased overall yields (Scheme 1.1).

Scheme 1.1. Linear (*E*)-allylic acetates through a C—H oxidation approach vs. traditional C—C bond forming reactions



The linear allylic oxidation developed in our lab proceeds with unprecedented levels of selectivity and generality offering clear synthetic advantages over traditional routes to linear allylic acetates. However, significant challenges remained that precluded its routine application (*i.e.* requirement for solvent quantities of nucleophile limiting its scope, superstoichiometric oxidant, high catalyst loading, moderate yields, and long reaction times) and presented exciting opportunities for further development and discovery. With these challenges in mind and a desire to test the hydrocarbon oxidation strategy in a more complex, densely functionalized setting, I undertook a project to advance and apply a more practical linear allylic C—H oxidation.

Scheme 1.2. A C—H oxidation strategy for polyol construction



Chiral (*E*)-2-butene-1,4-diols such as **1** are attractive building blocks that possess dense functionalization, a dissonant oxygen relationship,[9] and are easily elaborated through established olefin oxidation chemistry, such as the asymmetric dihydroxylation (Scheme 1.2). Compounds like **1** have been routinely employed as intermediates in natural product syntheses to install a diverse range of structures: *e.g.* 5- and 6-membered mono- and polycyclic ethers,[10] epoxyalcohols,[11] and, most extensively, contiguous polyol structures.[12] State-of-the-art syntheses of **1** based on Wittig-type olefinations[13] or cross-metathesis reactions[14] suffer from lengthy sequences, in part due to the difficulty in accessing highly enantioenriched α-hydroxy -aldehyde and -olefin starting materials. Alternatively, using a C—H oxidation approach, **1** may be synthesized directly from protected chiral homoallylic alcohols like **2** via the DMSO/Pd(II)-promoted allylic oxidation. The requisite starting materials for this strategy are stable and readily accessible *via* asymmetric allylation of aldehydes[15,16] or regioselective vinylation of chiral epoxides (Scheme 1.2).[17]

Significantly, 4-methoxybenzoate derivatives of chiral (*E*)-2-butene-1,4-diols (**1**) are unique among allylic alcohol derivatives in their ability to undergo asymmetric dihydroxylation with excellent reagent-controlled diastereoselectivity and minimal acyl transfer.[18] White and Fraunhoffer demonstrated in 2005, that the DMSO/Pd(II)-promoted linear allylic oxidation of protected chiral homoallylic alcohols with acetic acid furnishes acetate derivatives of chiral (*E*)-2-butene-1,4-diols in excellent regio- and stereoselectivities and no erosion in optical purity.[8] In order to avoid functional group manipulations and increase the nucleophile scope of the linear allylic oxidation, we set out to identify conditions wherein *p*-anisic acid (**4**) could be used as a nucleophile to *directly* generate 4-methoxybenzoate derivatives of **1** from α-olefins. Contained within this specific goal was the broader aim of improving the reactions practicality by seeking solutions to the challenges of the originally discovered system (*i.e.* nucleophile loading, nucleophile scope, moderate yield, high catalyst loading, and long reaction times)

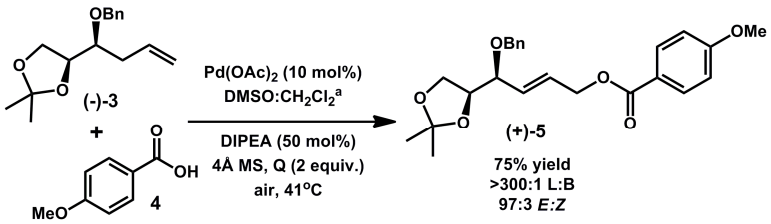
1.2 Results and Discussion

1.2.1 Reaction Optimization

As shown in Table 1.1, preliminary studies with α-olefin **3** suggested that acid **4** may be a competent nucleophile in the DMSO/Pd(II) linear allylic oxidation reaction to form (*E*)-2-butene-1,4-diol precursor **5** if the challenges associated with high acid loadings and low yields were resolved (15 equiv. **4**, 23% yield, Table 1.1, entry

1). We were encouraged by the observation that significant amounts of α-olefin starting material remained at the end of the reaction, suggesting that the acid labile acetonide functionality was tolerant of these conditions. The addition of *N*,*N*-diisopropylethylamine (DIPEA), a non-coordinating base additive, effected a significant increase in yield (45% yield, Table 1.1, entry 2). Although the exact role of the base is currently unclear, it is reasonable to hypothesize that it results in increased concentrations of the benzoate anion and thereby promotes functionalization. A second increase in yield was obtained by switching oxidants from benzoquinone to phenyl-benzoquinone (PhBQ, 55% yield, Table 1.1, entry 3). Finally, we observed that by increasing the reaction molarity to 2.0 M, we achieved further increases in yields and were able to use fewer equivalents of carboxylic acid (i.e. 2.0 M, 3 equiv. **4**, 75% yield, Table 1.1, entries 3-6).

Table 1.1. Evaluation of the linear allylic oxidation reaction to form the (*E*)-2-butene-1,4-diol precursor **(-)-3**.



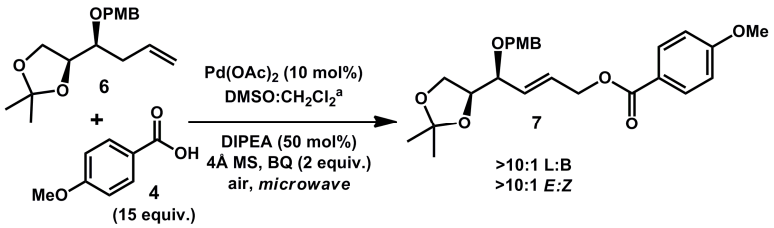
Entry	$DMSO:CH_2Cl_2$ Molarity (M)	Quinone (Q)	Acid (equiv.)	Isolated yield[c]
1	0.33 M	BQ	15	23%[d]
2	0.33 M	BQ	15	45%
3	0.33 M	PhBQ	15	55%
4	0.6 M	PhBQ	10	66%
5	1.0 M	PhBQ	5	67%
6[b]	2.0 M	PhBQ	3	75%
7[b]	2.0 M	PhBQ	3	71%[e]
8	2.0 M	PhBQ	3	63%[f]
9	3.0 M	PhBQ	1.5	50%

[a]$DMSO:CH_2Cl_2$ (3.2:1). [b]Linear to branched allylic ester L:B and *E*:*Z* ratios determined by HPLC for material obtained from entries 6 and 7 using authentic branched allylic ester and acetonide-deprotected *E* and *Z* allylic ester standards: L:B = >300:1; E:Z =30:1, 36:1 (entries 6 and 7, respectively). [c]Reactions done on a 1 mmol scale ((-)-**3**, 262 mg). Yields and selectivities represent an average of at least 2 runs. [d]No DIPEA (*N*,*N*-diisopropylethylamine) was added. [e]$Pd[CH_3CN]_4(BF_4)_2$ (10 mol%), 13% of (-)-**3** was recovered. [f]$Pd(OAc)_2$ (5 mol%).

The linear allylic oxidation reaction is exceptionally stereo- and regioselective with selective formation of the linear, *E*-isomer (L:B = >300:1; *E:Z* = 30:1 to 36:1; entries 6 and 7, Table 1.1). Using $Pd(OAc)_2$ as the Pd(II) source, the only observed byproduct in the reaction is the allylic acetate, which we found can be eliminated by using $Pd(CH_3CN)_4(BF_4)_2$, (Table 1.1, entry 7). This reaction is also preparatively convenient, with all reactions run under an air atmosphere with no precautions taken to exclude moisture or O_2. Significantly, with these newly developed

conditions the catalyst loading may be decreased to 5 mol% with only a minor decrease in yield (63% yield, Table 1.1, entry 8). Moreover, fragment coupling of the α-olefin with only 1.5 equiv. of carboxylic acid is possible in useful yields at higher concentration (3.0 M, 50%, Table 1.1, entry 9).

Table 1.2. Preliminary evaluation of microwave heating for improved reaction rates



Entry	Power (W)	Temperature (°C)	Time (min)	HPLC yield
1	30	41	15	<5%
2	100	41	15	23%
3	100	41	30	31%
4	150	41	15	29%
5	100	100	15	28%

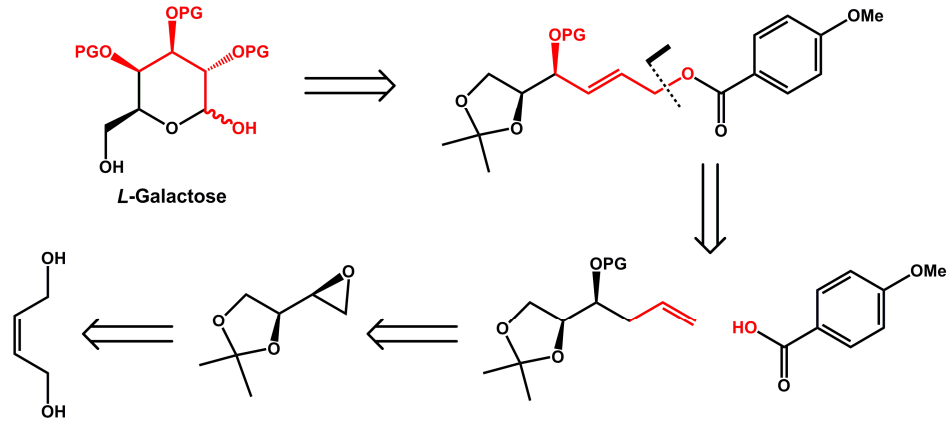
The optimized conditions described (*vide supra*) provide preliminary evidence that many of the practical challenges initially identified for the linear allylic oxidation may be addressed (*i.e.* nucleophile scope, nucleophile loading, and catalyst loading) without negatively impacting selectivities or functional group tolerance. However the reaction times for this system remained lengthy (72 hrs), and turnover rate would become more of a concern as catalyst loadings were reduced (Table 1.1, entry 6 vs. entry 8). While this problem has yet to be thoroughly addressed, preliminary investigations with the related α-olefin starting material **6** and acid **4** under microwave heating suggest a possible solution. After 15-30 minutes of heating with large excesses of acid nucleophile (15 equiv. **4**) yields of ~30% were obtained (Table 1.2, entries 3 & 4) while maintaining good levels of selectivity.

1.2.2 Enantioselective Total Synthesis of *L*-Galactose

Compounds analogous to **1** have been used as intermediates in several sterodivergent syntheses of the hexoses, an important class of polyols.[18a,19] I set out to test the efficiency of our allylic C—H oxidation strategy for polyol construction in the context of a short, *de novo* synthesis of differentially protected L-galactose (-)-**12** from a commercial, achiral starting material in which all new oxygen functionality would be installed *via* C—H and C=C bond oxidation reactions. I envisaged that *cis*-2-butene-1,4-diol could be converted to the key α-olefin starting material efficiently and on scale through epoxidation and subsequent rearrangement. Linear allylic C—H oxidation

followed by asymmetric dihydroxylation would afford the fully oxidized hexose core, and subsequent manipulations would lead to the desired differentially protected unnatural sugar (Scheme 1.3).

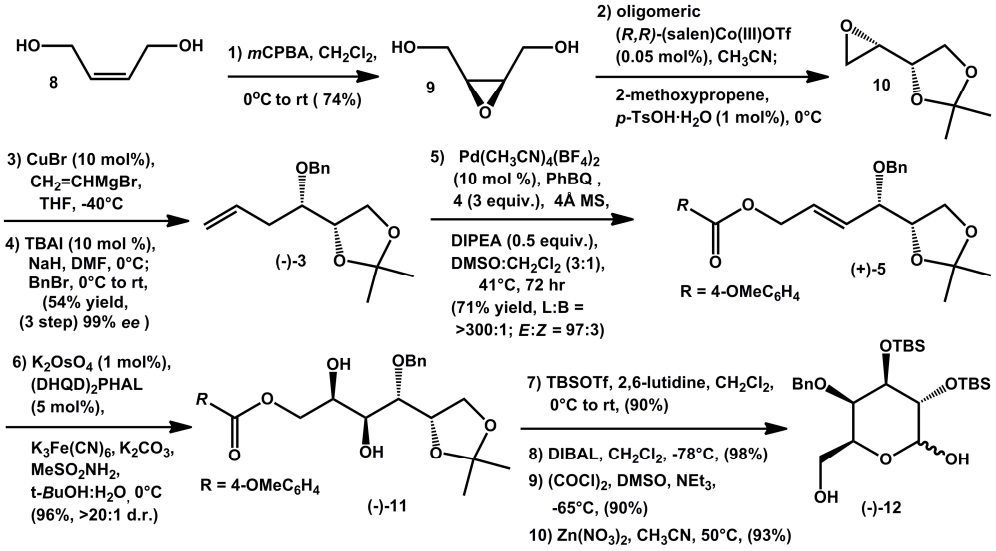
Scheme 1.3. Retrosynthesis of *L*-galactose utilizing linear allylic C—H oxidation



Bulk commodity chemical (*Z*)-2-butene-1,4-diol **8** was epoxidized with *m*-chloroperbenzoic acid to give *meso*-epoxide **9** in 74% yield. The reproducibility of epoxidation was significantly aided by the development of a washing procedure for commercially available *m*-chloroperbenzoic acid followed by titration of the resulting solution using NoD NMR. *Meso*-epoxide **9** was then desymmetrized *via* enantioselective Payne rearrangement with oligomeric (*R,R*)-(Salen)Co^{III}OTf catalyst (Salen = (*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine) and subsequently ketalized *in situ* to give chiral epoxyketal (*S,S*)-**10**.[20] This reaction has also been optimized with commercial (*R,R*)-(Salen)Co^{III}OAc (2 mol%) to give the desired chiral epoxyketal in 47% overall yield (95% *ee*). Lower yields were due to epoxide opening by MeOH during ketalization with higher catalyst loadings of the monomeric catalyst. Regioselective opening at the terminal position of the epoxyketal with vinylcuprate and ensuing benzyl protection of the intermediate alcohol gave protected homoallylic alcohol (-)-**3** in 54% overall yield (3-steps, 99% *ee*).[17,20b] Linear allylic C—H oxidation of (-)-**3** using 10 mol% $Pd(CH_3CN)_4(BF_4)_2$ under the optimized conditions (2M, PhBQ, 50 mol% DIPEA) with 3 equiv. of *p*-anisic acid **4** furnished 4-methoxybenzoate derived (*E*)-2-butene-1,4-diol (+)-**5** in 71% yield (w/ 13% recovered (-)-**3**) as essentially one isomer (L:B= >300:1; *E:Z* = 36:1) with no erosion of enantiopurity.[21] Alternatively, using 10 mol% $Pd(OAc)_2$ in DMSO under the same conditions, (+)-**5** was obtained in 75% yield with *ca.* 10% of the allylic acetate product that was arduous to separate via silica gel chromatography. Asymmetric dihydroxylation of (+)-**5** proceeded smoothly to give fully oxygenated (-)-**11** in 96% yield with >20:1 d.r. (^{1}H NMR).[22] *Bis*-silyl protection of diol (-)-**11** followed by DIBAL cleavage of the

p-methoxybenzoate ester, Swern oxidation of the resulting primary alcohol, and isopropylidene ketal removal with $Zn(NO_3)_2 \cdot 6H_2O$[23] gave differentially protected L-galactose (-)-**12** in 74% yield (4-steps).[24] This enantioselective, *de novo* synthesis of (-)-**12** proceeds in a total of 10 linear steps and 20% overall yield from commercial starting material **8**.

Scheme 1.4. Total synthesis of differentially protected L-galactose **(-)-12**



Interestingly, when a *para*-methoxybenzyl (PMB) group was used to protect the C3 alcohol instead of a benzyl group, the synthetic sequence suffered at several stages, though no difference was observed for the key allylic C—H oxidation step. In particular, the asymmetric dihydroxylation gave only 50% conversion (~45% yield) after 24 hours (versus 96% yield after 4 hours *vida supra*). The PMB group has been used as an alternative to 4-methoxybenzoates as an agent for interacting with asymmetric dihydroxylation ligands, suggesting that it may competitively interact with the catalyst and slow the reaction. Furthermore, attempts to perform the final deprotection/cyclization of this sequence were unsuccessful due to significant deprotection or migration of the PMB group under all conditions evaluated for acetonide removal.

1.3 Conclusions

A number of stereodivergent, *de novo* syntheses of the hexoses from **8** have employed chiral (*E*)-2-butene-1,4-diols analogous to **5** as intermediates. The C—H oxidation route to **5** (5 steps, 28% overall yield) compares favorably with the Wittig-olefination routes of the previously reported syntheses with respect to number of steps and

overall yield (11 steps, 18% overall yield[18a]; 9 steps, 16% overall yield[19]). Analogous to these previous syntheses, the strategy developed herein provides access to hexose stereoisomers that are complementary to those obtained through aldol-based approaches.[25]

In summary, a mild and efficient hydrocarbon oxidation strategy for the preparation of chiral polyols has been presented and validated through an enantioselective synthesis of differentially protected L-galactose ((-)-**12**). This synthesis was enabled by the development of a highly regio- and stereoselective linear allylic C—H oxidation reaction that generates 4-methoxybenzoate derivatives of chiral (*E*)-2-butene-1,4-diols directly from readily available protected chiral homoallylic alcohols and carboxylic acids. We anticipate that the structurally simplifying and mild nature of this transform (i.e. **1** ⇒ **2**, Scheme 1.2) will render it generally useful in the synthesis of polyoxygenated motifs in the context of complex molecules.[26]

1.4 Experimental Section

General Information: All commercially obtained reagents were used as received: 2-phenyl-1,4-benzoquinone (ACROS); $Pd(CH_3CN)_4(BF_4)_2$, $Pd(OAc)_2$, $K_2OsO_4 \cdot 2H_2O$, (1R,2R)-(-)-[1,2-Cyclohexanediamino-N,N'-bis(3,5-di-t-butylsalicylidene)]Cobalt(II) (Strem Chemicals). Palladium was stored in a glove box under an argon atmosphere and weighed out in the air prior to use. Solvents tetrahydrofuran (THF), diethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Anhydrous N, N-dimethylformamide (DMF) (Sure/Seal) was obtained from Sigma-Aldrich and used as received. (*Z*)-2-butene-1,4-diol (Fluka) was used as received. All allylic oxidation reactions were run under air with no precautions taken to exclude moisture. All other reactions were run under a balloon of argon gas unless otherwise stated. Achiral gas chromatographic (GC) analyses were performed on Agilent Technologies 6890N Series instrument equipped with FID detectors using a HP-5 (5%-Phenyl)-methylpolysiloxane column (30m, 0.32mm, 0.25μm). HPLC analysis was performed on an Agilent Technologies 1100 HPLC system with a model 1100 Quaternary Pump, Diode Array Detector, Thermostat, and Autosampler. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, potassium permanganate, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still et al.[27] using EM reagent silica gel 60 (230-400 mesh). ^{1}H NMR spectra were recorded on a Varian Unity 400 (400 MHz) or a Varian Unity 500 (500 MHz), or a Varian Unity

Inova 500NB spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration, corresponding carbon atom. Proton-decoupled ^{13}C- NMR spectra were recorded on a Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX and are reported in frequency of absorption (cm^{-1}). All optical rotations were determined on a Perkin Elmer 341 Polarimeter using the sodium D line (589 nm). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory.

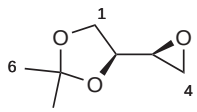
Representative Procedure for the $Pd(CH_3CN)_4(BF_4)_2$ catalyzed Linear Allylic C—H Oxidation of (-)-3 to (+)-5. To a 40 mL borosilicate vial was added sequentially the following: $Pd(CH_3CN)_4(BF_4)_2$ (44.4 mg, 0.1 mmol, 10 mol%), phenyl benzoquinone (368 mg, 2.0 mmol, 2 equiv.), *p*-anisic acid (456 mg, 3.0 mmol, 3 equiv.), 4Å molecular sieves (200 mg), DMSO (0.380 mL), CH_2Cl_2 (0.120 mL), DIPEA (0.122 mL, 0.7 mmol, 0.7 equiv.), and a Teflon© stir bar. The vial was then capped and stirred at 41°C for 1 hour. The vial was cooled to room temperature and **(-)-(3)** (262 mg, 1 mmol, 1 equiv.) was added. The vial was capped and stirred at 41°C for 72 hours. Care was taken in charging and stirring to keep all reagents off of the walls and contained at the bottom of the vial and in maintaining the temperature centered at 41°C (i.e. 40°C-43°C). Upon completion, the reaction was quenched with sat. aq. NH_4Cl solution (1 mL), stirred for 30 minutes, and then transferred to a separatory funnel using ethyl acetate (10 mL). Hexanes (40 ml) was added and the organics were washed with H_2O (50 mL) and 5% aq. Na_2CO_3 solution (2 x 50 mL). (Note: Upon addition of hexanes a significant amount of phenyldihydroquinone will crash out of solution as a black solid. This solid is readily removed in the next step during filtration.) The organic layer was dried ($MgSO_4$), filtered, and reduced *in vacuo*. Subsequent transfers were all performed using ether to minimize transfer of phenyldihydroquinone. Purification via flash silica gel chromatography (30% Et_2O/hexanes) gave 0.309 g of (+)-(**5**) as an amber oil: (Run 1 = 71% yield; run 2 = 69% yield; run 3 = 74% yield) **Average = 71% yield**. Approximately 13% of (-)-**3** was also recovered. Linear to branched and *E:Z* ratios were determined as described above and found to be similar to those determined for $Pd(OAc)_2$ (L:B = >300:1; *E:Z* = 36:1).

(3-Hydroxymethyl-oxiranyl)-methanol (9)

To 35 g of ≤77% pure *m*-chloroperbenzoic acid (Aldrich) in a 1 L separatory funnel was added dry CH_2Cl_2 (250 mL). The solution was washed with 1:1 sat. aq. $NaHCO_3$:H_2O solution (2 x 100 mL) and

then dried over Na_2SO_4 until the liquid became translucent (~ 1 hr). The solution was then filtered into a clean, dry 1 L round bottom flask pre-marked at approximately 380 mL volume. Dry CH_2Cl_2 was added to bring the total volume up to this mark and a 0.65 ml aliquot was removed and titrated using No-D NMR with a known amount of $CHCl_3$ (~50 µL) as the internal standard.[28] By this analysis, the solution was determined to contain 15 g (87.2 mmol, 1.1 equiv.) of mCPBA. A Teflon© stir bar was added and the atmosphere exchanged for nitrogen. The solution was cooled to 0°C and (*Z*)-2-butene-1,4-diol (**8**) (6.85 mL, 79.3 mmol, 1 equiv.) was added via syringe. The reaction was allowed to warm to room temperature and became a milky color within one hour. After 16 hours of stirring, the CH_2Cl_2 was removed via rotary evaporation, dry ether (300 mL) was added, and the material was stirred 3 hours at room temperature, after which the reaction flask was placed in a -20°C freezer for 1 hour. The resulting solids were filtered off and rinsed with cold, dry ether (5 x 50 mL). The filtrate was left in the freezer overnight to give a second harvest of crystals which were also filtered and washed with dry, cold ether to give a total of 6.16 g of a fine white powder (**9**) (74%).

^{1}H NMR (500 MHz, CD_3OD) δ 3.73 (dd, J = 3.5, 12.3 Hz, 2H, C1), 3.59 (dd, J = 7.0, 12.3 Hz, 2H, C1), 3.14 - 3.11 (m, 2H, C2); **^{13}C NMR** (125 MHz, CD_3OD) δ 61.2, 57.8.[29]



(2S,3S)-3,4-epoxy-1,2-di-O-isopropylidenebutane-1,2-diol (10)

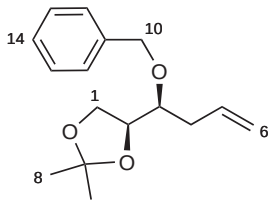
Method A: [oligomeric (*R,R*)-(Salen)-Co^{III}OTf]

To a clean, dry 100 mL round bottom flask with a Teflon© stir bar was added (**9**) (5.0 g, 48.0 mmol, 1 equiv.), oligomeric (*R,R*)-(Salen)Co^{III}OTf (0.019 g, 0.05 mol%), and CH_3CN (24 mL). The reaction was vigorously stirred under air until ~70% conversion of starting material was observed (^{1}H NMR of an aliquot from the reaction mixture in CD_3OD; ratio of m @ 3.12 ppm vs. dd @ 2.69 ppm + dd @ 2.76 ppm) (~12 hrs). The reaction mixture was then cooled to 0°C and 2-methoxypropene (5.53 mL, 5.77 mmol, 1.2 equiv.) was added followed by *p*-TsOH · H_2O (0.091 g, 0.480 mmol, 0.01 equiv.). The reaction was stirred at 0°C for 1 hour and then the solvents removed slowly (~45 min.) via rotary evaporation at 0°C. The reaction mixture was loaded neat onto a silica column and purified via flash silica gel chromatography (10%-20%-30%-40% Et_2O/pentane). Removal of the column solvent via distillation at 55°C gave a crude mixture of (**10**) (~4.67 g, 68% yield by ^{1}H NMR) and the seven-membered ketal product that was taken forward without further purification.[30] (Note: The purity of the starting material for this

reaction has a large effect on catalyst loading and overall yield. Inferior batches of (**9**) should be purified via flash silica gel chromatography in 10%-15% MeOH/CH_2Cl_2 prior to use.)

Method B: [commercial (*R,R*)-(Salen)-$Co^{III}OAc$][31]

To a clean, dry 250 mL round-bottom flask with a Teflon© stir bar was added (**9**) (2.0 g, 19.2 mmol, 1 equiv.) and (*R,R*)-(Salen)$Co^{III}OAc$ (0.255 g, 2 mol%). THF (9.6 mL) was added and the reaction was vigorously stirred under air until ~70% conversion of starting material was observed (^{1}H NMR of an aliquot from the reaction mixture in CD_3OD; ratio of m @ 3.12 ppm vs. dd @ 2.69 ppm + dd @ 2.76 ppm)(~12 hrs). The solvent was then removed via rotary evaporation, and dry acetone (9.6 mL) was added. The reaction flask was cooled to 0°C and 2,2-dimethoxypropane (5.7 mL, 48.0 mmol, 2.5 equiv.) was added followed by slow addition of pyridinium *p*-toluenesulfonic acid (1.21 g, 4.80 mmol, 25 mol%). The reaction was allowed to warm to room temperature and then taken to 50°C for 24 hours. After stirring 24 hours, the reaction mixture was cooled to room temperature, transferred to a 1L separatory funnel, and Et_2O (200 mL) and sat. aq. $NaHCO_3$ (25 mL) were added. The aqueous layer was then back extracted [5 x (100 mL Et_2O + 4 mL THF)] and the combined organics distilled slowly away at 55°C. Flash silica gel chromatography (10%-20%-30% Et_2O/pentane) followed by distillation of the column solvent at 55°C afforded a crude mix of (**10**) (~1.35 g, 49% yield by ^{1}H NMR) and the seven-membered ketal product that was taken on without further purification.[30] $\mathbf{R_f}$ = 0.206 (20% Et_2O/Pentane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.10 (dd, J = 6.5, 8.5 Hz, 1H, C1), 3.97 (app. q, J= 6.5, 1H, C2), 3.85 (dd, J = 6.5, 8.5 Hz, 1H, C1), 3.03 (ddd, J = 2.5, 4.3, 5.6 Hz, 1H, C3), 2.80 (dd, J = 4.0, 5.0 Hz, 1H, C4), 2.67 (dd, J = 2.5, 5.3 Hz, 1H, C4), 1.44 (s, 3H, acetonide CH_3), 1.36 (s, 3H, acetonide CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 110.0, 76.2, 65.9, 52.0, 43.8, 26.4, 25.5; **LRMS** (CI) m/z calculated for $C_7H_{13}O_3$ $[M + H]^+$: 145.1; found 145.1.[32]

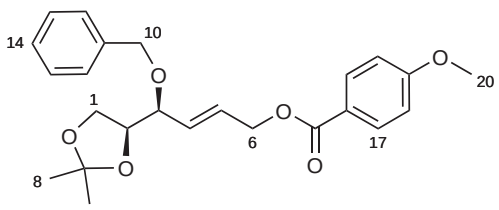


(2S,3S)-3-O-benzyl-1,2-di-O-isopropylidene-5-hexen-1,2,3-triol (-)-(3)

To a clean, dry 100 mL flask with a Teflon© stir bar and under an argon atmosphere was added copper (I) bromide (0.228 g, 1.59 mmol, 0.1 equiv.) and 12 mL dry THF. The reaction flask was covered with aluminum foil to prevent exposure to light and cooled to -40°C. Freshly prepared vinylmagnesium bromide[33] was then added (28.3 mL of a 0.618 M solution in THF, 1.1 equiv.) and the reaction mixture stirred for 10 minutes. A solution of the crude mix of (**10**) (~2.29 g, 15.9 mmol, 1

equiv.) and the corresponding seven-membered ketal in dry THF (3.75 mL initial volume, 2 x 2.1 mL rinses) at -40°C was then added via cannula, and the reaction stirred at -40°C in the dark for 1 hour. A quench of sat. aq. NH_4Cl solution (15 mL) was added and stirred vigorously as the reaction was allowed to warm to room temperature. Et_2O (100 mL) was added, and the aqueous layer extracted [5 x (50 mL Et_2O + 4 mL THF)]. The combined organics were washed with H_2O (50 mL) and the aqueous layer again back extracted [3 x (50 mL Et_2O + 4 mL THF)]. After drying (Na_2SO_4) and filtering, the solvent was distilled away at 65°C.

To a clean, dry 250 mL round bottom flask was added sodium hydride (0.762 g, 31.8 mmol, 2 equiv.), TBAI (0.507 g, 1.6 mmol, 0.1 equiv.), and anhydrous DMF (50 mL). This flask was cooled to 0°C, and then the reaction mixture containing the crude alcohol from above in DMF (10 mL initial volume, 2 x 5 mL rinses) at 0°C was added dropwise via cannula. The reaction was stirred 1 hour at 0°C and then benzyl bromide (2.02 mL, 16.7 mmol, 1.05 equiv.) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred until TLC revealed complete conversion of starting material (~1 hr). Upon completion, the reaction flask was cooled to 0°C and H_2O (50 mL) was added. The flask was stirred an additional 5 minutes, and then Et_2O (200 mL) was added. The aqueous layer was extracted with Et_2O (3 x 50 mL), the combined organic layers were dried ($MgSO_4$), filtered, and reduced *in vacuo*. Flash silica gel chromatography (1%-2%-3%-5% EtOAc/hexanes) afforded 3.32 g of **(-)-(3)** (80% 2 steps) as a clear liquid in 99% ee (HPLC, Chiralcel AD-RH, 50% CH_3CN/H_2O, 0.5 mL/min., t_R(minor) = 14.2 min., t_R(major) = 15.5 min.). $\mathbf{R_f}$ = 0.392 (10% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.31 (m, 4H, C12,C13), 7.30–7.26 (m, 1H, C14), 5.88 (ddt, J = 7.5, 10.0, 17.0 Hz, 1H, C5), 5.11 (dm, J = 17 Hz, 1H, C6), 5.07 (dm, J = 17 Hz, 1H, C6), 4.72 (d, J = 12.0 Hz, 1H, C10), 4.66 (d, J = 11.5 Hz, 1H, C10), 4.21 (app. q, J = 7.0, 1H, C2), 3.99 (dd, J = 6.5, 8.0 Hz, 1H, C1), 3.71 (app. t, J = 7.8 Hz, 1H, C1), 3.51 (dt, J = 4.5, 6.8 Hz, 1H, C3), 2.31 (m, 1H, C4), 2.23 (m, 1H, C4), 1.43 (s, 3H, acetonide CH_3), 1.37 (s, 3H, acetonide CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.6, 134.5, 128.3, 127.8, 127.5, 117.2, 109.3, 79.2, 77.9, 72.5, 65.8, 35.3. 26.5, 25.4; **IR** (neat, cm^{-1}) 3066.5, 3023.3, 2986.1, 2935.0, 2878.6, 1641.7, 1455.0, 1071.6; **HRMS** (ESI) m/z calculated for $C_{16}H_{22}O_3Na$ $[M + Na]^+$: 285.1467; found: 285.1480. $[\alpha]^{22}_D$ = -15.6° (c = 1.1, $CHCl_3$); lit. $[\alpha]^{20}_D$ = +13.9° (c = 1.1, $CHCl_3$) (enantiomer).[34]



(2S,3S)-(E)-3-O-benzyl-1,2-di-O-isopropylidene-4-hexen-6-(4-methoxyphenylbenzoate)-1,2,3-triol (+)-(5)

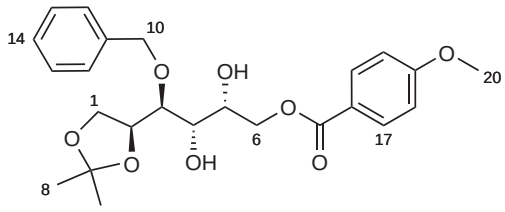
Method A: $Pd(OAc)_2$

To a 40 mL borosilicate vial was added sequentially the following: $Pd(OAc)_2$ (0.0224 g, 0.1 mmol, 10mol%), phenyl benzoquinone (0.368 g, 2.0 mmol, 2 equiv.), *p*-anisic acid (0.456 g, 3.0 mmol, 3 equiv.), 4Å molecular sieves (0.200 g), (-)-**(3)** (0.262 g, 1 mmol, 1 equiv.), DMSO (0.380 mL), CH_2Cl_2 (0.120 mL), diisopropylethylamine (0.087 mL, 0.5 mmol, 0.5 equiv.) and a Teflon© stir bar. The vial was then capped and stirred at 41°C for 72 hours. Care was taken in charging and stirring to keep all reagents off of the walls and contained at the bottom of the vial and in maintaining the temperature centered at 41°C (i.e. 40°C-43°C). Upon completion, the reaction was quenched with sat. aq. NH_4Cl solution (1 mL), stirred for 30 minutes, and then transferred to a separatory funnel using ethyl acetate (10 mL). Hexanes (40 ml) was added and the organics were washed with H_2O (50 mL) and 5% aq. Na_2CO_3 solution (2 x 50 mL). (Note: Upon addition of hexanes a significant amount of phenyldihydroquinone will crash out of solution as a black solid. This solid is readily removed in the next step during filtration.) The organic layer was dried ($MgSO_4$), filtered, and reduced *in vacuo*. Subsequent transfers were all performed using ether to minimize transfer of phenyldihydroquinone. Purification via flash silica gel chromatography (30% Et_2O/hexanes) gave 0.309 g of (+)-(**5**) as an amber oil. (Run 1 = 74% yield; run 2 = 76% yield) **Average = 75% yield**. Linear to branched ratios (>300:1) were determined by HPLC using authentic branched allylic product[3a,c] (Agilent Zobrax Eclipse XDB-C8, 35% *i*-PrOH/H_2O, 1 mL/min., t_R (linear) = 15.7 min., t_R (branched) = 18, 19 min. (two diastereomers)). E:Z (30:1) ratios were determined by HPLC using acetonide deprotected *E* and authentic *Z* isomers (Symmetry C-18, 40%CH_3CN/H_2O, 1.0 mL/min., t_R (*E*) = 10.1 min., t_R (*Z*) = 11.3 min.) Using this procedure, 0.032 g (10%) of the linear acetate product was also formed and could not be readily separated from (+)-(**5**).

Method B : $Pd(CH_3CN)_4(BF_4)_2$

To a 40 mL borosilicate vial was added sequentially the following: $Pd(CH_3CN)_4(BF_4)_2$ (0.044 g, 0.1 mmol, 0.1 equiv.), phenyl benzoquinone (0.368 g, 2.0 mmol, 2 equiv.), *p*-anisic acid (0.456 g, 3.0 mmol, 3 equiv.), 4Å molecular sieves (0.200 g), DMSO (0.380 mL), CH_2Cl_2 (0.120 mL), diisopropylethylamine (0.122 mL, 0.7 mmol, 0.7 equiv.), and a Teflon© stir bar. The vial was then capped and stirred at 41°C for 1 hour. The vial was cooled to room temperature and (-)-(**3**) (0.262 g, 1 mmol, 1 equiv.) was added. The vial was capped and stirred at 41°C for 72

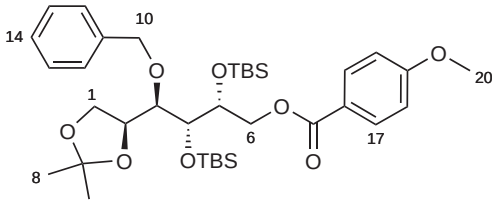
hours. Care was taken in maintaining the temperature centered at 41°C (i.e. 40°C-43°C) and in charging and stirring to keep all reagents off of the walls and contained at the bottom of the vial. After 72 hours, the reaction was quenched with sat. aq. NH_4Cl solution (1 mL), stirred for 30 minutes, and then transferred via pipette to a separatory funnel using ethyl acetate (10 mL). Hexanes (40 ml) was added and the organics were washed with H_2O (50 mL) and 5% aq. Na_2CO_3 solution (2 x 50 mL). The organic layer was dried ($MgSO_4$), filtered, and reduced *in vacuo*. Purification via flash silica gel chromatography (30% Et_2O/hexanes) gave 0.293 g of (+)-(**5**) as an amber oil with 13% recovered starting material. (Run 1 = 71% yield; run 2 = 69% yield; run 3 = 74% yield) **Average = 71% yield**. Linear to branched and E: Z ratios were determined as described above and found to be similar to those determined for $Pd(OAc)_2$ (L:B = >300:1, E:Z = 36:1). $\mathbf{R_f}$ = 0.17 (30% Et_2O/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.0 (app. dt, J = 2.5, 9.0 Hz, 2H, C17), 7.36–7.25 (m, 5H, C12, 13, 14), 6.93 (app. dt, J = 2.5, 9.0 Hz, 2H, C18), 5.97 (ddt, J = 1.0, 5.5, 15.8 Hz, 1H, C5), 5.74 (ddt, J = 1.5, 8.0, 15.8 Hz, 1H, C4), 4.82 (app. d, J = 5.5 Hz, 2H, C6), 4.68 (d, J = 12.0 Hz, 1H, C10), 4.50 (d, J = 12.0 Hz, 1H, C10), 4.22 (app. q, J = 6.5 Hz, 1H, C2), 3.96 (dd, J = 6.5, 8.5 Hz, 1H, C1), 3.91 (app. t, J = 7.0 Hz, 1H, C1), 3.87 (s, 3H, C20), 3.77 (dd, J = 6.0, 8.8 Hz, 1H, C3), 1.39 (s, 3H, acetonide CH_3), 1.35 (s, 3H, acetonide CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.9,163.4, 138.1, 131.7, 129.9, 129.8, 128.3, 127.8, 127.6, 122.4, 113.6, 109.7, 79.7, 77.3, 70.5, 65.7, 64.0, 55.4, 26.4, 25.3; **IR** (neat, cm^{-1}) 2985.3, 2934.8, 2873.4, 1713.2, 1606.5, 1511.5, 1256.9; **HRMS** (ESI) m/z calculated for: $C_{24}H_{29}O_6$ $[M + H]^+$: 413.1964, observed: 413.1960; $[\alpha]^{22}_D$ = +72.5° (c = 1.0, $CHCl_3$).



3-O-benzyl-1,2-di-O-isopropylidene-6-(4-methoxyphenylbenzoate)-L-galacitol (-)-(11)

To a clean, dry 50 mL recovery flask was added sequentially the following: $K_2OsO_4 \cdot 2H_2O$ (0.007 g, 0.019 mmol, 1 mol%), $(DHQD)_2PHAL$ (0.076 g, 0.095 mmol, 5 mol%), $K_3Fe(CN)_6$ (1.89 g, 5.72 mmol, 3 equiv.), K_2CO_3 (0.792 g, 5.72 mmol, 3 equiv.), a Teflon© stir bar, deionized water (9.5 mL), and *tert*-butanol (5 mL). The reaction flask was stirred vigorously until both layers became translucent, at which time $MeSO_2NH_2$ (0.187 g, 1.91 mmol, 1 equiv.) was added and the reaction was cooled to 0°C. After the solution became opaque, olefin (+)-(**5**) (0.787 g, 1.91 mmol, 1 equiv.) was added dropwise via pipette in *tert*-butanol (1.5 mL initial volume, 2 x 1 mL rinses) and the reaction was stirred vigorously at 0°C until completion as indicated by TLC (~3.5 hr). Upon completion, sodium

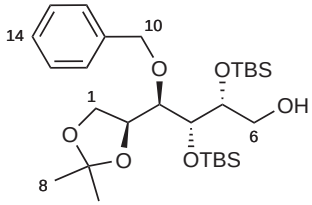
bisulfite (1.81 g) was added slowly and the reaction was allowed to warm to room temperature and stir for 1 hour. EtOAc (10 ml) was added and the aqueous layer extracted with additional EtOAc (3 x 15 mL). The combined organic layers were washed with 2N KOH (1x10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification via flash silica gel chromatography (40% EtOAc/hexanes) afforded 0.818 g (96%) of (-)-(**11**) as a clear, viscous oil. $\mathbf{R_f}$ = 0.190 (40% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ7.99 (app. dt, J = 2.5, 9.0 Hz, 2H, C17), 7.37-7.28 (m, 5H, C12, C13, C14), 6.92 (app. dt, J = 2.5, 9.0 Hz, 2H, C18), 4.79 (d, J = 11.5 Hz, 1H, C10), 4.71 (d, J = 11.0 Hz, 1H, C10), 4.40 (dd, J = 5.0, 6.0 Hz, 1H, C2), 4.44-4.35 (m, 2H, C6), 4.19 (app. q, J = 6.5 Hz, 1H, C5), 4.05 (dd, J = 6.5, 8.5 Hz, 1H, C1), 3.86 (s, 3H, C20), 3.85 (app. t, J = 8.0, 1H, C1), 3.74-3.69 (m, 2H, C3/C4), 3.11 (d, J = 5.5 Hz, 1H, OH), 2.81 (d, J = 6.0 Hz, 1H, OH), 1.45 (s, 3H, acetonide CH_3), 1.37 (s, 3H, acetonide CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.6, 163.6, 137.8, 131.8, 128.5, 128.1, 128.0, 122.0, 113.7, 109.3, 78.9, 77.0, 74.4, 70.5, 68.7, 66.0, 65.9, 55.4, 26.3, 25.3; **IR** (neat, cm^{-1}) 3455.5, 2985.2, 2935.9, 1713.2, 1606.5, 1581.4, 1512.3, 1258.5; **HRMS** (ESI) m/z calculated for $C_{24}H_{31}O_8$ $[M + H]^+$: 447.2019; found 447.2012; $[\alpha]^{22}_D$ = -16.5° (c = 1.0, $CHCl_3$).



3-O-benzyl-4,5-di-O-(*tert*-butyldimethylsilanyloxy)-1,2-di-O-isopropylidene-6-(4-methoxyphenylbenzoate)-L-galacitol

To (-)-(**11**) (0.818 g, 1.83 mmol, 1 equiv.), in a 50 mL recovery flask under nitrogen with a Teflon© stir bar, was added dry CH_2Cl_2 (12.2 mL). The flask was cooled to 0°C and 2,6-lutidine (1.28 mL, 11.00 mmol, 6 equiv.) was added. *Tert*-butyldimethylsilyl triflate (1.26 mL, 5.50 mmol, 3 equiv.) was then added dropwise over 15 minutes with vigorous stirring. The reaction was stirred at 0°C for 20 minutes, then allowed to warm to room temperature and monitored via TLC. Upon completion (~40 min.), the reaction was again cooled to 0°C, H_2O (5 mL) was added slowly, and the reaction stirred 15 minutes to quench. EtOAc (10 mL) was added and the aqueous layer was extracted with additional EtOAc (3 x 15 mL). The combined organic layers were washed with H_2O (1 x 5 mL), sat. aq. $NaHCO_3$ solution (1 x 5 mL), with H_2O (1 x 5 mL), then dried (Na_2SO_4), filtered, and reduced *in vacuo*. Purification via flash silica gel chromatography (2%-3%-5% EtOAc/hexanes) afforded 1.11 g (90%) of the title compound as a clear, viscous oil. $\mathbf{R_f}$ = 0.320 (10% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (app. d, J = 8.5 Hz, 2H, C17), 7.40 (d, J = 7.5 Hz, 2H, C12), 7.31 (t, J = 7.5 Hz, 2H, C13), 7.26-7.22 (m, 1H, C14), 6.91 (app. d, J = 8.5 Hz, C18),

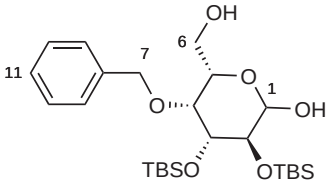
4.83 (d, J = 12.0 Hz, 1H, C10), 4.80 (d, J = 12.0 Hz, 1H, C10), 4.62 (dd, J = 3.5, 11.5 Hz, 1H, C6), 4.52 (dd, J = 7.0, 9.0 Hz, 1H, C2), 4.50 (dd, J = 7.5, 14.8 Hz, 1H, C6), 4.09 (dt, J = 3.4, 7.0 Hz, 1H, C5), 4.06 (dd, J = 6.5 Hz, 9.0 Hz, 1H, C1), 3.86 (s, 3H, C20), 3.77 (app. t, J = 3.5 Hz, 1H, C4), 3.69 (app. t, J = 7.0Hz, 1H, C1), 3.60 (dd, J = 3.5, 7.8 Hz, 1H, C3), 1.43 (s, 3H, acetonide CH_3), 1.35 (s, 3H, acetonide CH_3), 0.93 (s, 9H, TBS CCH_3), 0.87 (s, 9H, TBS CCH_3), 0.13 (s, 3H, TBS CH_3), 0.12 (s, 3H, TBS CH_3), 0.06 (s, 3H, TBS CH_3), 0.05 (s, 3H, TBS CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.1, 163.2, 138.9, 131.6, 128.2, 127.7, 127.3, 122.8, 113.5, 108.9, 83.7, 76.6, 74.9, 74.6, 73.8, 66.7, 66.7, 55.4, 26.8, 25.9, 25.7, 25.3, 18.2, 18.0, -4.0, -4.4, -4.7, -4.8; **IR** (neat, cm^{-1}) 2954.9, 2930.8, 2887.0, 2858.0, 1716.6, 1606.9, 1581.8, 1512.0; **HRMS** (ESI) m/z calculated for $C_{36}H_{58}O_8NaSi_2$ $[M + Na]^+$: 697.3568; found 697.3573; $[\alpha]^{22}_D$ = +31.2° (c =1.0, $CHCl_3$).



3-O-benzyl-4,5-di-O-(*tert*-butyldimethylsilanyloxy)-1,2-di-O-isopropylidene-L-galacitol

To the fully protected L-galacitol (1.05 g, 1.56 mmol, 1 equiv.) in a clean, dry 50 mL flask with a Teflon© stir bar under an argon atmosphere was added dry CH_2Cl_2 (2.85 mL) and the flask was cooled to -78°C. Diisobutylaluminum hydride (1.0 M in CH_2Cl_2, 3.89 mL, 2.5 equiv.) was added dropwise and the reaction was stirred vigorously at -78°C. Upon completion (~ 1 hr), -78°C EtOAc (5 mL) was added followed by sat. aq. Rochelle's salts (15 mL). The reaction was allowed to warm to room temperature and then stirred an additional thirty minutes. H_2O (25mL) and CH_2Cl_2 (20 mL) were added and the aqueous layer extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and reduced *in vacuo*. The residue was purified via flash silica gel chromatography (7% EtOAc/hexanes) to give 0.823 g (98%) of the title compound as a clear oil. $\mathbf{R_f}$ = 0.267 (10% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (app. d, J = 7.0 Hz, 2H, C12), 7.32 (app. t, J = 7.0 Hz, 2H, C13), 7.29-7.24 (m, 1H, C14), 4.90 (d, J = 11.5 Hz, 1H, C10), 4.77 (d, J = 11.0 Hz, C10), 4.60 (dt, J = 7.0, 8.5 Hz, 1H, C2), 4.08 (dd, J = 7.0, 8.3 Hz, 1H, C1), 3.80 (ddd, J = 3.0, 5.5, 11.6 Hz, 1H, C6), 3.73 (app. q, J = 4.0 Hz, 1H, OH), 3.70-3.64 (m, 1H, C6), 3.66, (dd, J = 3.0, 4.5 Hz, 1H, C4), 3.61 (dd, J = 3.0, 9.0 Hz, 1H, C3), 3.58 (app. t, J = 8.0 Hz, 1H, C1), 3.26 (app. dd, J = 5.5, 7.8 Hz, 1H, C5), 1.44 (s, 3H, C8/C9), 1.35 (s, 3H, C8/C9), 0.91 (s, 9H, TBS CCH_3), 0.90 (s, 3H, TBS CCH_3), 0.10 (s, 3H, TBS CH_3), 0.10 (s, 6H, TBS CH_3), 0.08 (s, 3H, TBS CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.3, 128.3, 127.9, 127.6, 108.9,

85.5, 76.5, 75.9, 75.2, 74.8, 66.9, 62.0, 26.9, 25.9, 25.8, 25.4, 18.2, 18.0, -4.2, -4.7, -4.9, -4.9; **IR** (neat, cm^{-1}) 3474.6, 2954.3, 2930.5, 2886.5, 2858.1, 1472.0; **HRMS** (ESI) m/z calculated for $C_{28}H_{53}O_6Si_2$ $[M + H]^+$: 541.3381; found 541.3376; $[\alpha]^{22}_D = +7.2°$ (c =1.0, $CHCl_3$).

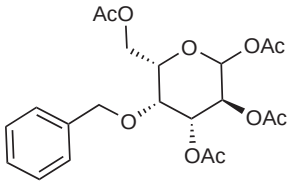


4-O-benzyl-2,3-di-O-(*tert*-butyldimethylsilanyloxy)-L-galactopyranose (-)-(12)

To a clean, dry 10 mL round bottom flask with a Teflon© stir bar and an argon atmosphere was added oxalyl chloride (0.161 mL, 1.9 mmol, 1.25 equiv.) and dry CH_2Cl_2 (4.9 mL). The reaction flask was cooled to -65°C ($CHCl_3$, dry ice) and 0.671 mL of a 5.1M DMSO solution (3.42 mmol, 2.25 equiv.) in dry CH_2Cl_2 was added and stirred for 10 minutes. The differentially protected galacitol (0.823 g, 1.52 mmol, 1 equiv.) in dry CH_2Cl_2 (1.6 mL initial volume, 2 x 0.33 mL rinse) was then added dropwise via cannula, and the reaction stirred at -65°C for 20 minutes. Triethylamine (0.90 mL, 6.47 mmol, 4.25 equiv.) was added dropwise, the reaction was stirred 15 minutes at -65°C, then allowed to warm to room temperature, and stirred an additional 10 minutes. Water (5 mL) was added and the reaction mixture transferred to a separatory funnel. The aqueous layer was extracted with $CHCl_3$ (3 x 15 mL), the combined organics were dried (Na_2SO_4), filtered, and reduced *in vacuo*. Conversion of the primary alcohol to the aldehyde was checked by ^1H NMR in C_6D_6 and determined to be ~90%.

To the crude aldehyde was added CH_3CN (6.6 mL) and $Zn(NO_3)_2 \cdot 6H_2O$ (1.25 g, ~5 equiv.). The reaction was then taken to 50°C and monitored via TLC. Upon completion (~12hrs) the flask was cooled and the CH_3CN removed via rotary evaporation. Water (3 mL) and CH_2Cl_2 (10 mL) were added and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were then dried (M_gSO_4), filtered, and reduced *in vacuo*. Purification by flash chromatography (1% MeOH/CH_2Cl_2) gave 0.637 g of a white crystalline solid (-)-(**12**) (84% 2-steps). $\mathbf{R_f}$ = 0.104 (1%CH_2Cl_2); (Note: The product exists as a mixture of anomers, α:β = 3:2, with the β anomer as a mixture of two conformers[35]) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H α, 10H β), 5.21 (t, J = 3.5 Hz, 1H, C1 α), 4.98 (d, J = 11.0 Hz, 1H β), 4.93 (d, J = 11.5 Hz, 1H, C7 α), 4.75 (d, J = 11.5 Hz, 1H β), 4.69 (dd, J = 3.5, 9.8 Hz, 1H β), 4.60-4.56 (m, 2H β), 4.59 (d, J = 12.0 Hz, 1H, C7 α), 4.34 (d, J = 10.0 Hz, 1H β), 4.08 (ddd, J = 2.0, 5.0, 7.1 Hz, 1H, C6 α), 4.03-3.96 (m, 2H β), 4.01 (dd, J = 3.0, 8.0 Hz, 1H, C2/C3 α), 3.98 (dd, J = 2.5, 8.0 Hz, 1H, C2/C3 α), 3.96-3.91 (m, 2H β), 3.91-3.86 (m, 2H β), 3.88 (ddd, J = 4.0, 7.0, 11.4 Hz, 1H, C6 α), 3.84-3.82 (m, 2H β), 3.81-3.78 (m, 1H β), 3.80 (t, J = 2.5 Hz, 1H, C4 α), 3.75-3.65 (m, 3H β), 3.65 (ddd, J = 5.0, 8.5, 11.5 Hz, 1H, C6

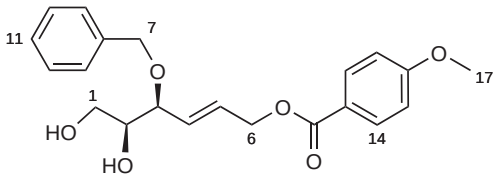
α), 3.56-3.51 (m, 1H β), 3.23 (dd, J = 4.5, 9.0 Hz, 1H β), 2,99 (d, J = 4.0 Hz, OH α), 2.62 (dd, J = 3.0, 10.0 Hz, 1H β), 1.92-1.90 (m, 1H β), 1.91 (dd, J = 3.5, 9.0 Hz, 1H, OH α), 0.95-0.87 (m, 18H α, 36H β), 0.16-0.08 (m, 12H α, 24 H β); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.3, 137.9, 137.5, 128.5, 128.4, 128.1, 128.0, 128.0, 127.9, 127.8, 92.4, 81.4, 77.4, 76.7, 75.9, 75.3, 74.5, 74.3, 74.2, 74.1, 73.3, 72.9, 72.2, 71.4, 70.7, 64.0, 62.6, 62.0, 60.8, 29.7, 26.1, 26.0, 25.9, 25.8, 25.7, 18.1, 18.1, 17.9, -4.0, -4.1, -4.3, -4.5, -4.7, -4.8, -4.8, -4.9, -5.0; **IR** (neat, cm^{-1}) 3417.8, 2956.1, 2929.7, 2894.1, 2857.6, 1472.; **HRMS** (ESI) m/z calculated for $C_{25}H_{46}O_6NaSi_2$ $[M + Na]^+$: 521.2731; found 521.2740; $[\alpha]^{22}_D$ = -28.1° (c =1.0, $CHCl_3$).



1,2,3,6-O-tetraacetyl-4-O-benzyl-L-galactopyranose

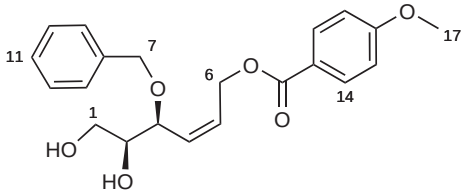
To a clean, dry 10 mL recovery flask under a nitrogen atmosphere with a Teflon© stir bar was added (-)-(**12**) (0.200 g, 0.401 mmol, 1 equiv.) and CH_2Cl_2 (2 mL). The reaction flask was cooled to 0°C and acetic anhydride (0.190 mL, 2.01 mmol, 5 equiv.), triethylamine (0.560 mL, 4.01 mmol, 10 equiv.) and 2,2-dimethylaminopyridine (0.005 g, 0.04 mmol, 0.1 equiv.) were added. The reaction was then stirred at 0°C for 30 minutes, room temperature for 1 hour, and then at reflux for 5 hours. The reaction mixture was then transferred to a separatory funnel and EtOAc (15 mL) was added. The organic layer was washed with 1 M HCl (1 x 15 mL), 10% aq. $NaHCO_3$ solution (15 mL), and brine (15 mL). The organic layer was then dried (Na_2SO_4), filtered, and reduced *in vacuo*. THF (0.5 mL) was added to this crude residue along with a Teflon© stir bar and the reaction flask was cooled to 0°C. Tetra-n-butylammonium fluoride (1.0 M in THF, 1.9 mL, 4.75 equiv.) was added slowly, and then the reaction was allowed to warm to room temperature and monitored via TLC. Upon completion, sat. aq. NH_4Cl solution (5 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and reduced *in vacuo* to give a brown residue, which was subsequently dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C. A Teflon© stir bar, acetic anhydride (0.190 mL, 2.01 mmol, 5 equiv.), triethylamine (0.560 mL, 4.01 mmol, 10 equiv.) and 2,2-dimethylaminopyridine (0.005 g, 0.04 mmol, 0.1 equiv.) were added. The reaction mixture was again stirred at 0°C for 30 minutes, room temperature for 1 hour, and then at reflux for 5 hours. The reaction mixture was then cooled to room temperature and transferred to a separatory funnel with EtOAc (15 mL). The reaction mixture was then washed with 1 M HCl (1 x 15 mL), 10% aq. $NaHCO_3$ solution (15 mL), and brine (15 mL). The organic layer was then dried (Na_2SO_4), filtered, and reduced *in vacuo* to give a thick brown oil. Purification via flash silica

gel chromatography (40%EtOAc/hexanes) afforded 0.173 g of a white, foamy oil (98%) as a mixture of anomers (α:β = 55:45). $\mathbf{R_f}$ = 0.434 (40%EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.30 (m, 5H α and 5H β), 6.36 (d, J = 3.5 Hz, 1H α), 5.16 (d, J = 8.0 Hz, 1H β), 5.53 (dd, J = 3.5, 11.0 Hz, 1H α), 5.50 (dd, J = 8.0, 10.5 Hz, 1H β), 5.29 (dd, J = 3.0, 11.0 Hz, 1H α), 5.01 (dd, J = 3.0, 10.5 Hz, 1H β), 4.75 (d, J = 11.5 Hz, 1H β), 4.73 (d, J = 11.0 Hz, 1H β), 4.55 (d, J = 11.5 Hz, 1H α), 4.54 (d, J = 11.5 Hz, 1H α), 4.24-4.15 (m, 2H α and 1H β), 4.13-4.05 (m, 2H α and 1H β), 3.98-3.94 (m, 1H β), 3.86-3.83 (m, 1H β), 2.13, 2.10, 2.05, 2.04, 2.04, 2.02, 2.01, 2.0 (8s, 12 H α and 12H β); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.4, 170.3, 170.3, 170.2, 169.8, 169.3, 169.1, 169.0, 137.2, 137.1, 128.6, 128.5, 128.5, 128.3, 128.1, 128.1, 92.1, 89.9, 75.2, 75.0, 74.2, 73.6, 73.1 ,73.0, 70.4, 70.3, 68.4, 66.9, 62.2, 62.0, 20.9, 20.8, 20.7, 20.7, 20.6, 20.5; **HRMS** (ESI) m/z calculated for: $C_{21}H_{26}O_{10}Na$ $[M + Na]^+$: 461.1424, observed: 461.1431.[36]



(2S,3S)-(E)-3-O-benzyl-4-hexen-6-(4-methoxyphenylbenzoate)-1,2,3-triol

To a 1 dram vial was added (+)-(**5**) (0.041 g, 0.1 mmol, 1 equiv.), CH_3CN (2 mL) and $Zn(NO_3)_2 \cdot 6H_2O$ (0.097 g, 0.19 mmol, 5 equiv.). A Teflon© stir bar was added to the reaction vessel and the reaction was then taken to 50°C and monitored via TLC. Upon completion (~24hrs) the flask was cooled and the CH_3CN removed via rotary evaporation. Water (1 mL) and CH_2Cl_2 (5 mL) were added and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were then dried (M_gSO_4), filtered, and reduced *in vacuo*. Purification by flash silica gel chromatography in 2% MeOH/CH_2Cl_2 gave 0.025 g of the title compound as a clear oil (70%). $\mathbf{R_f}$ = 0.10 (1%CH_2Cl_2/MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.0 (app. dt, J = 3.0, 8.5 Hz, 2H, C14), 7.38–7.28 (m, 5H, C9, 10, 11), 6.94 (app. dt, J = 2.5, 9.0 Hz, 2H, C15), 6.03 (ddt, J = 1.0, 5.5, 15.8 Hz, 1H, C5), 5.80 (ddt, J = 1.5, 8.0, 15.3 Hz, 1H, C4), 4.86 (app. dd, J = 1.5, 5.5 Hz, 2H, C6), 4.67 (d, J = 11.0 Hz, 1H, C7), 4.38 (d, J = 11.5 Hz, 1H, C7), 3.94 (app. t, J = 7.5 Hz, 1H, C3), 3.87 (s, 3H, C17), 3.74-3.69 (m, 1H, C1/C2), 3.68-3.66 (m, 1H, C1/C2), 3.62-3.57 (m, 1H, C1/C2), 2.84 (d, J= 3.0 Hz, 1H, OH), 2.07 (t, J = 6.0 Hz, 1H, OH); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.9,163.5, 137.6, 131.7, 130.5, 129.9, 128.5, 128.0, 128.0, 122.3, 113.7, 80.2, 73.7, 70.6, 63.9, 63.0, 55.4; **HRMS** (ESI) m/z calculated for: $C_{21}H_{25}O_6$ $[M + H]^+$: 373.1651, observed: 373.1654.



(2S,3S)-(Z)-3-O-benzyl-4-hexen-6-(4-methoxylphenylbenzoate)-1,2,3-triol

Authentic Z isomer of (+)-(**5**) for determination of the E:Z selectivity of the linear allylic C-H oxidation reaction was prepared through the following sequence: (-)-(**11**) was subjected to periodate cleavage to give a terminal aldehyde,[37] followed by Still-Gennari olefination to give the (*Z*)-α,β-unsaturated methyl ester,[38] which was reduced to the alcohol with diisobutylaluminum hydride, converted to the 4-methoxyphenylbenzoate derivative through dicyclohexylcarbodiimide assisted coupling with *p*-anisic acid, and finally acetonide deprotected with $Zn(NO_3) \cdot 6H_2O$. $\mathbf{R_f}$ **=** 0; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (app. dt, J = 3.0, 9.0 Hz, 2H, C14), 7.37-7.28 (m, 5H, C9/C10/C11), 9.92 (app. dt, J = 3.0, 9.0 Hz, 2H, C13), 6.02 (dt, J = 6.5, 11.0 Hz, 1H, C5), 5.63 (dt, J = 1.5, 10.5 Hz, 1H, C4), 4.90 (ddd, J = 1.5, 7.0, 13.4 Hz, 1H, C6), 4.84 (ddd, J = 1.5, 6.5, 13.5 Hz, 1H, C6), 4.67 (d, J = 11.5 Hz, 1H, C7), 4.42 (d, J = 11.5 Hz, 1H, C7), 4.38 (dd, J = 7.5, 9.5 Hz , 1H, C2), 3.86 (s, 3H, C17), 3.72-3.78 (m, 1H, C1), 3.70-3.64 (m, 1H, C3), 3.63-3.56 (m, 1H, C1), 2.93 (b s, 1H, OH), 2.25 (b s, 1H, OH); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.1, 163.5, 137.6, 131.8, 131.7, 130.6, 128.6, 128.0, 127.7, 122.2, 113.7, 75.4, 73.7, 70.7, 62.8, 60.5, 55.4

1.5 References

[1] A portion of this work was summarized in a previous publication: Dustin J. Covell, Nicolaas A. Vermeulen, Nathan A. Labenz, and M. Christina White *Angew. Chem. Int. Ed.* **2006**, 45, 8217 – 8220. The data in Table 1.1 was generated in collaboration with Nicolaas A. Vermeulen.

[2] (a) Wender, P.A.; Hilinski, M.K.; Mayweg, A.V.W. *Org. Lett.* **2005**, *7*, 79. (b) Zhang, Q.; Rich, J.O.; Cotterill, I.C.; Pantaleone, D.P.; Michels, P.C. *J. Am. Chem. Soc.* **2005**, *127*, 7286. (c) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510. (d) Dangel, B.D.; Godula, K.; Youn, S.W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856. (e) Breslow, R.; Baldwin, S.; Flechter, T.; Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc.* **1973**, *95*, 3251.

[3] General C—H oxidation, aminations, alkylations: (a) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (b) Espino, C. G.; DuBois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 379. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439, and references therein. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (e) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (f) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (g) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (h) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090. (i) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015. (j) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (k) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (l) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566. (m) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.Eur. J.* **2010**, *16*, 2654. (n) Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W. *Science* **2006**, *312*, 1941. (o) Engelin, C. J. and Fristrup, P. *Molecules* **2011**, *16*, 951 and references therein.

[4] Pd-catalyzed allylic C—H oxidations: (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (b) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (c) Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032. (d) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076. (e) see ref 1. (f) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481. (g) Pilarski, L. T.; Selander, N.; Bose, D.; Szabo, K. J. *Org. Lett.* **2009**, *11*, 5518. (h) Lin, B.-L.; Labinger, J. A.; Bercaw, J. E. *Can. J. Chem.* **2009**, *87*, 264. (i) Thiery, E.; Aouf, C.; Belloy, J.; Harakat, D.; Le Bras, J.; Muzart, J. *J. Org. Chem.* **2010**, *75*, 1771. (j) Henderson, W. H.; Check, C. T.; Proust, N.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 824. (k) Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 15116.

[5] Pd(II)/AcOH: (a) Hansson, S.; Heumann, A.; Rein, T.; Akermark, B. *J. Org. Chem.* **1990**, *55*, 975. (b) Heumann, A.; Reglier, M.; Waegell, B. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 366. (c) Heumann, A.; Akermark, B. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 453. (d) McMurry, J. E.; Kocovsky, P. *Tetrahedron Lett.* **1984**, *25*, 4187. (e) Akermark, B.; Larsson, E. M.; Oslob, J. D. *J. Org. Chem.* **1994**, *59*, 5729. (f) Macsari, I.; Szabo, K. J. *Tetrahedron Lett.* **1998**, *39*, 6345. SeO2/*t*-BuOOH: (g) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. Cu(I)/*tert*butyl perbenzoate: (h) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845.

[6] (a) Grennberg, H.; Backvall, J.-E. *Chem. Eur. J.* **1998**, *4*, 1083. (b) Wolfe, S.; Campbell, P. G. C. *J. Am. Chem. Soc.* **1971**, *93*, 1497, 1499. (c) Kitching, W.; Rappoport, Z.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1966**, *88*, 2054. (d) Trost, B. M.; Metzner, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3572.

[7] Pd(II)/DMSO/O2: (a) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am.Chem. Soc.* **2002**, *124*, 766. (b) Grennberg, H.; Gogoll, A.; Backvall, J.- E. *J. Org. Chem.* **1991**, *56*, 5808.

[8] K.J. Fraunhoffer, D.A. Bachovchin, M.C. White, *Org. Lett.* **2005**, *7*, 223.

[9] For an explanation of the term dissonant relationship see: Evans, D.A.; Andrews, G.C. *Acc. Chem. Res.* **1974**, *7*, 147.

[10] For example: (a) Jiang, L.; Burke, S. D. *Org. Lett.* **2002**, *4*, 3411. (b) Smith III, A. B.; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 196.

[11] For example: Crimmins, M. T.; Caussanel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3128.

[12] For example: (a) Trost, B. M.; Wrobleski, S. T.; Chisholm, J. D.; Harrington, P. E.; Jung, M. *J. Am. Chem. Soc.* **2005**, *127*, 13589. (b) Ikemoto, N.; Schreiber, S.L. *J. Am. Chem. Soc.* **1992**, *114*, 2524.

[13] For example see: Tsuboi, K.; Ichikawa, Y.; Naganawa, A.; Isobe, M.; Ubukata, M.; Isono, K. *Tetrahedron* **1997**, *53*, 5083.

[14] (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (b) Keller, V. A.; Kim, I.; Burke, S. D. *Org. Lett.* **2005**, *7*, 737.

[15] Chiral (*E*)-2-buten-1,4-diols with good to moderate enantio-selectivities *via* allylation with chiral (*E*)-γ- ($PhMe_2Si$) allylboronate reagents followed by epoxidation /Petersen elimination: (a) W.R. Roush, P.T. Grover, *Tetrahedron Lett.* **1990**, *31*, 7567. (b) Roush, W. R.; Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett.* **2000**, *41*, 9413.

[16] Representative asymmetric allylation reactions: (a) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 2554. (b) Denmark, S. E.; Fu, J.; Lawler, M. J. *J. Org. Chem.* **2006**, *71*, 1523. (c) Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 946. (d) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401. (e) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186.

[17] Mukai, C.; Kim, J. S.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2903.

[18] (a) Guzman-Perez, A.; Corey, E. J. *Tetrahedron Lett.* **1997**, *38*, 5941. (b) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805.

[19] (a) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed III, L. A.; Sharpless, K. B.; Walker, F. J. *Science*, **1983**, 949. (b) Ko, S. K.; Lee, A. W. M.; Masamune, S.; Reed III, L. A.; Sharpless, K. B.; Walker F. J. *Tetrahedron* **1990**, *46*, 245.

[20] (a) White, D. E.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **2003**, *14*, 3633. (b) Stevenson, C. P. Ph.D. thesis, Harvard University, Cambridge, Massachusetts **2005**; (c) Ready, J. M.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2002**, *41*, 1374. (d) Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2012.

[21] The diastereomer that corresponds to racemization of the allylic center was independently synthesized and was not detected by HPLC analysis (see experimental section for details).

[22] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

[23] Vijayasaradhi, S.; Singh, J.; Aidhen, I. *Synlett* **2000**, *1*, 110.

[24] (-)-**12** was silyl deprotected and peracetylated to give 1,2,3,6-O-tetraacetyl-4-O-benzyl-L-galactopyranose that was found to be spectroscopically identical to the known compound (see experimental section for details): Ermolenko, L.; Sasaki, N. A. *J. Org. Chem.* **2006**, *71*, 693.

[25] Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752.

[26] Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 481.

[27] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[28] Hoye, T. R.; Eklov, B. M.; Ryba, T. D.; Voloshin, M.; Yao, L. J. *Org. Lett.* **2004**, *6*, 953.

[29] Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38* 2012.

[30] (a) White, D. E. and Jacobsen, E. N. *Tetrahedron: Asymmetry*, **2003**, *14*, 3633-3638. (b) ref. 20b

[31] Commercially available (1R,2R)-(-)-[1,2-Cyclohexanediamino-*N*,*N*'-bis(3,5-di-t-butylsalicylidene)]Cobalt(II) can be oxidized to the Co(III)OAc species using AcOH in CH_2Cl_2. see ref. 29

[32] Abushanab, E.; Vemishetti, P,; Leiby, R. W.; Singh, H. K.; Amarendra, B.; Mikkilineni, D. C. J.; Wu, R. S.; Panzica, R. P. *J. Org. Chem.* **1988**, *53*, 2598.

[33] Seyferth, D. *Organic Syntheses*, **1959,** *39*, 10.

[34] Cossy, J.; Willis, C.; Bellosta, V.; Bouz Bouz, S. *J. Org. Chem.* **2002,** *67*, 1982.

[35] Yamada, H.; Tanigakiuchi, K.; Nagao, K.; Okajima K.; Mukae, T. *Tetrahedron Lett.* **2004,** *45*, 9207.

[36] Ermolenko, L.; Sasaki, N. A. *J. Org. Chem* **2006**, *71*, 693.

[37] Schmid, C. R.; Bryant, J. D. *Organic Syntheses* **1998**, *9*, 450.

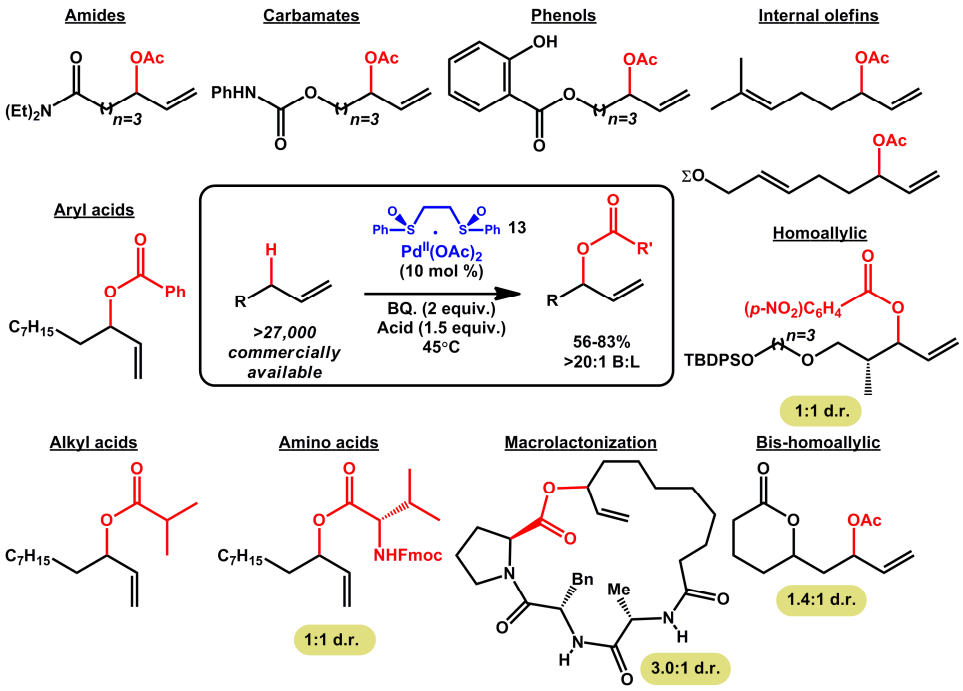
[38] (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (b) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248.

A Chiral Lewis Acid Co-Catalyst Strategy for Enantioselective Allylic C—H Oxidation[40]

2.1. Introduction

Polyoxygenated natural products and medicinally interesting compounds are ubiquitous, and a host of methods for manipulating and transforming these molecules are available. However, most methods require significant synthetic overhead, commonly in the form of protection/deprotection steps and functional group manipulations. Selective hydrocarbon oxidation presents an alternative approach by directly increasing molecular complexity when it is most synthetically appropriate, reducing the number of reactive functional groups carried through a sequence.[41,42,43] However, in order to be useful for complex molecule synthesis, these reactions must proceed with high levels of chemo-, regio- and stereoselectivity.

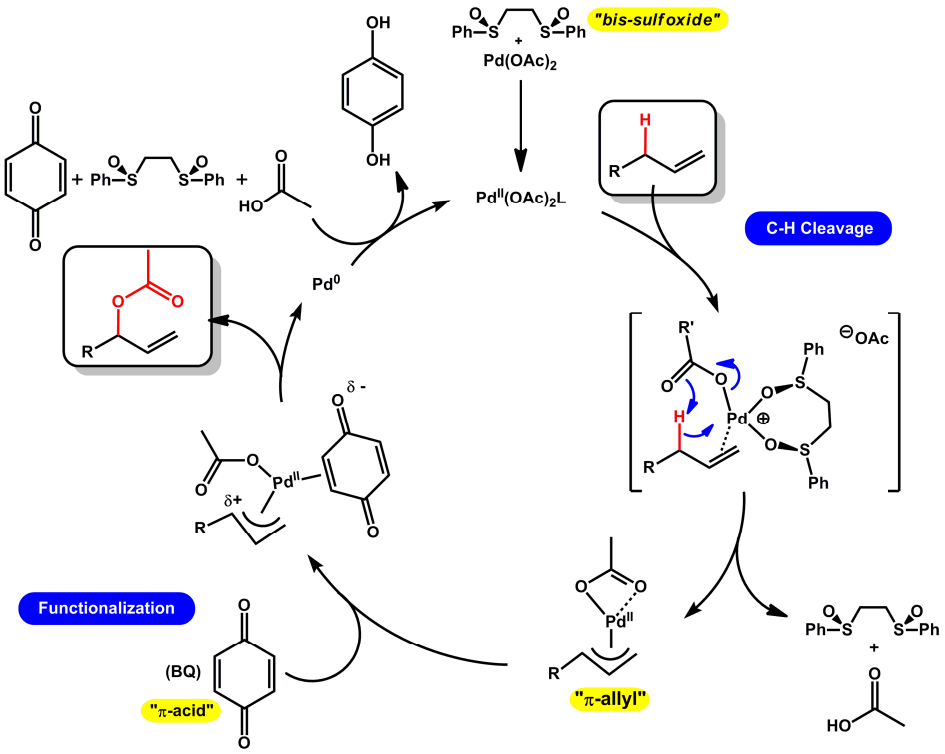
Figure 2.1. Catalytic branched allylic oxidation of α-olefins with $Pd(OAc)_2$/PhBS (**13**)



In 2005, Chen and White reported a sulfoxide-promoted, catalytic $Pd(OAc)_2$/benzoquinone (BQ)/α-olefin allylic oxidation system that furnishes branched allylic alkyl and aryl esters from a wide variety of carboxylic acids (Figure 2.1).[42a-b] Additionally, they were able to show that these reactions proceed via a novel serial ligand catalysis mechanism. A sulfoxide ligand and a π-acid ligand were found to interact sequentially with Pd to shepherd the

metal center through C—H cleavage and C—O bond-forming steps, respectively. The sulfoxide ligand is believed to interact with palladium, partially displace its carboxylate ligands, and generate a transient electrophilic Pd(II) species capable of promoting C—H cleavage through an intramolecular deprotonation. C—O bond formation likely occurs via a benzoquinone (BQ) promoted inner-sphere reductive elimination of acetate to an electronically dissymmetric π-allyl-Pd intermediate (Scheme 2.1).[44]

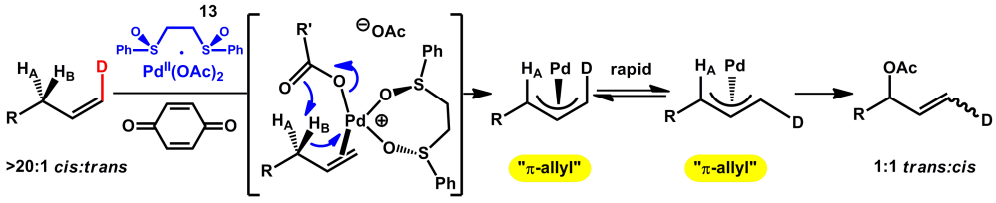
Scheme 2.1. Serial ligand catalysis mechanism



While the branched allylic oxidation was found to proceed with excellent yields and selectivities on a variety of substrates,[42a-d,43b,e] the reaction as discovered generates a racemate. Furthermore, initial investigations with chiral substrates, α-olefin or acid nucleophile, generated products with virtually no diastereoselectivity (Figure 2.1). Enantioselective allylic C—H activation has been achieved with chiral bisoxazoline/copper catalyzed systems, showing promising levels of asymmetric induction in enantioselective allylic C—H esterifications of symmetrical, cyclic olefins. Application of these systems to complex substrates is limited by a lack of chemo- and regioselectivity and the requirement for large excesses of substrate (4 to 10 equiv.).[45] A more general allylic C—H oxidation route would significantly increase the efficiency of chiral allylic alcohol/ester syntheses, which often require lengthy sequences of functional group manipulations from pre-oxidized materials.[46,47]

Conventional approaches to asymmetric organometallic reactions make use of strongly coordinating, σ-donating, chiral ligands, such as phosphines. These types of ligands are poorly suited for reaction under oxidative conditions and outcompete the weakly coordinating sulfoxide and quinone ligands required for C—H activation with palladium catalyst **13**.[48] The transient nature of ligand binding under serial ligand catalysis adds significant challenge to designing a highly ordered environment around the metal center, though in theory, a chiral variant of either the sulfoxide or quinone ligand could lead to enantioenriched products. To date, all attempts with chiral sulfoxides have been unsuccessful in effecting asymmetric induction. Experiments with *cis*-1-deutero-1-decene reveal that this is most likely due to rapid π-σ-π isomerization of the π-allyl-Pd intermediate, which scrambles any chiral information imparted during the C—H cleavage step (Scheme 2.2). I therefore set out to identify a viable strategy for enantioselective C—O bond formation. The obvious platform for an asymmetric functionalization ligand, benzoquinone, is impractical for covalent chiral modification as it is required in superstoichiometric amounts for optimal reactivity.

Scheme 2.2. Deuterium labeling study to establish relative rates of π-σ-π isomerization and functionalization

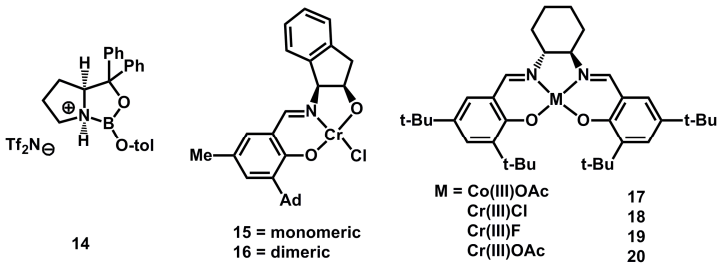


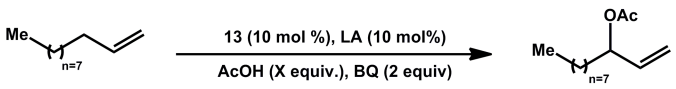
Lewis acid co-catalysts have been demonstrated to accelerate bond forming reactions from organometallic intermediates.[49] I postulated that a chiral Lewis acid co-catalyst could be used to both accelerate the rate of C—O bond formation and influence its stereochemical course from a π-allyl-Pd-BQ intermediate. Specifically, it was envisioned that coordination of an oxophilic, chiral Lewis acid to the carbonyl of BQ would increase the π-acidity of the ligand, accelerating C—O bond formation while transmitting chiral information to the palladium center. This would afford enantioenrichment despite background reactivity. In addition, I hypothesized that chiral Lewis acids with tightly binding ligands and lacking *cis* open coordination sites would be compatible with C—H activation conditions. Specifically, I reasoned that this particular class of Lewis acids would have ligand environments resistant to perturbation by the acid nucleophile and would be unlikely to irreversibly bind the *bis*-sulfoxide ligand, allowing it to interact with palladium and promote C—H cleavage.

2.2 Results and Discussion

2.2.1 Discovery, Optimization, and Scope

Table 2.1. Analysis of Lewis acid mediated enantioselective C—H bond oxidation





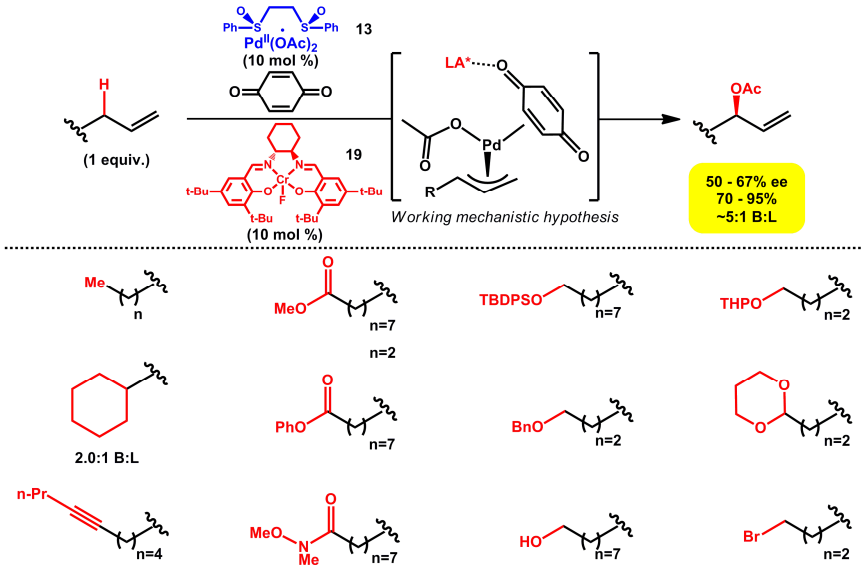
Entry	LA	M	X	T	% Yield [a]	B:L	ee [b]
1	-	0.33	4	45	71	>30:1	0
2	14	0.33	4	45	27	28:1	0
3	15	0.33	4	45	7	8:1	0
4	16	0.33	4	45	41	6:1	0
5	17	0.33	4	45	6	>30:1	0
6 [c]	17	2	1.1	rt	1	1.9:1	4
7 [d]	17	2	1.1	rt	4	2.8:1	14
8	18	0.33	4	45	7	1.2:1	32
9	18	0.33	1.1	45	10	1.2:1	32
10	18	2	1.1	rt	35	1.1:1	32
11 [d]	18	2	1.1	rt	41	1.4:1	32
12	19	0.33	4	45	74	9.3:1	9
13	19	0.33	1.1	45	59	7.9:1	15
14	19	2	1.1	rt	86	4.6:1	54
15 [d]	19	2	1.1	rt	93	5.1:1	57
16	20	0.33	4	45	11	3.2:1	8
17	20	0.33	1.1	45	8	2.0:1	14
18	20	2	1.1	rt	50	1.5:1	29
19 [d]	20	2	1.1	rt	71	2.0:1	31

[a]GC yield, average of at least two runs [b]Determined by Chiral GC [c]TBME, 1.1 equiv. DIPEA [d]EtOAc solvent, 4Å MS bead added(~30 mg), 48 hrs.

I began by examining chiral Lewis acids known to catalyze highly enantioselective reactions via a single point binding mode to Lewis basic carbonyl groups. Of the catalysts evaluated, commercially available (Salen)$Cr^{III}Cl$ complex **18**[50] was the only to afford any enantioselectivity for the process, albeit with diminished conversion and regioselectivity (Table 2.1, entries 1 vs. 2-5, 8). *R,R*-Salen-Co^{III}-OAc was also found to give slight enantioselectivity (entry 6) when run under conditions previously used to deliver carboxylate nucleophiles to *meso*-epoxides.[51] Analysis of several counterions for the Cr^{III} metal center revealed that (Salen)$Cr^{III}F$ (**19)** had a more

desirable conversion and regioselectivity, albeit with reduced enantioselectivity (entry 8 vs. 12). Increasing the concentration of the reaction, reducing the equivalents of acetic acid, changing solvent, and decreasing the temperature afforded a significant enhancement in enantioselectivity for reaction with **19** (entries 13-15) giving 57% *ee* with excellent yields and good regioselectivity. Interestingly, catalyst **18** showed no change in enantioselectivity over any conditions tested. I synthesized and tested a variety of other Salen-type chromium Lewis acid catalysts, but found none that were significantly better than the commercially available 3,5-di-*t*-butylsalicylidene ligand framework.[52] The enantioselection observed for this reaction is the highest for the allylic C—H oxidation of terminal olefins to date.[53] Additionally, to the best of my knowledge, this represents the first example of a chiral Lewis acid effecting asymmetric induction from an organometallic intermediate and a rare example of a catalytic enantioselective C—H functionalization using palladium.[54]

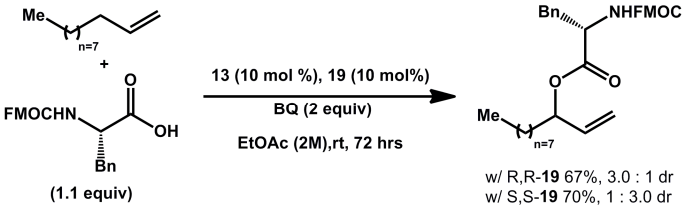
Figure 2.2. Scope of the catalytic, asymmetric, branched allylic oxidation of α-olefins with **13** and **19**



The scope and functional group tolerance of this system were then evaluated. Comparison of the product formed from the reaction of octene with *R,R*-**19** as catalyst to acetylated commercially available Matasuka alcohol ((*S*)-1-octen-3-ol, Fluka, >99% ee) established that the allylic stereocenter was *R*, while *S,S*-**19** afforded *S* product. Careful monitoring of the reaction showed that the regio- and stereoselectivity were not changing over time. Gratifyingly, the functional group tolerance of this system matches that of the original Pd^{II}/bis-sulfoxide methodology with tolerance for esters, amides, a wide variety of protected alcohols, free alcohols, internal alkynes, and aliphatic halogens (Figure 2.2). As steric bulk was brought closer to the allylic position, a modest variation in

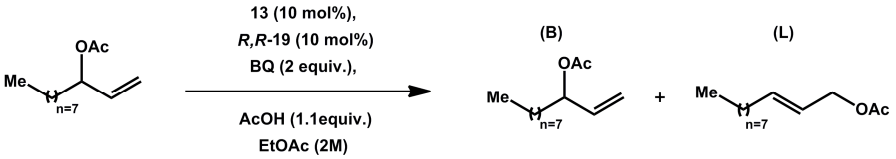
enantiomeric excess and a more significant change in the regioselectivity was observed. A variety of carboxylate nucleophiles could be successfully employed in this reaction as well, including chiral, protected amino acids such as *L*-FMOC-phenylalanine, which affords ~70% yield of a diastereomeric mixture (3.0:1) of products after 72 hrs of reaction with **13** and *R,R*-**19**. The stereocenter of the amino acid is inconsequential to the reaction as, employing catalyst *S,S*-**19** affords a complete reversal of diastereoselectivity (Scheme 2.3). Consistent with the continued role of BQ as a ligand for promoting functionalization, sterically hindered 2,6-dimethylbenzoquinone gave only trace reactivity in the catalytic reaction.

Scheme 2.3. Asymmetric branched allylic oxidation with amino acid nucleophile



2.2.2 Mechanistic Investigation

Table 2.2. Mechanistic evaluation of Lewis acid as an agent for enantioselective allylic acetate rearrangement

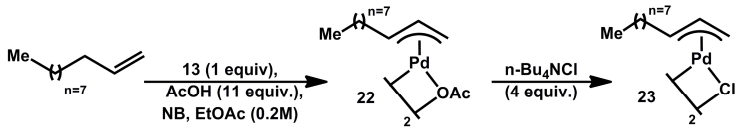


Entry	Modifications	t=0 B:L	t=24 B:L	t=24 %ee
1	-	>99:1	96:4	0
2	0.5 equiv. allylcyclohexane	>99:1	>99:1	0
3	0.5 equiv. allylcyclohexane BQ (1 equiv.). DHQ (1 equiv.) AcOH (0.1 equiv.)	>99:1	>99:1	0
4	no Pd	>99:1	>99:1	0
5	no 13	>99:1	98:2	0

At this point, I began to investigate the mechanism of this Lewis acid co-catalyzed allylic C—H activation reaction. My working mechanistic hypothesis was that the chromium Lewis acid was interacting with BQ and increasing the rate of functionalization. Testing this hypothesis and determining the mode of action of the Lewis acid catalyst in this system, would allow me to validate this novel mode of effecting asymmetric induction and promoting reactivity under electrophilic, oxidative conditions. I first evaluated the stability of the allylic acetate

products in the reaction to determine if the enantioselection observed was due to a racemic C—H activation/functionalization with subsequent enantioselective rearrangement. No significant isomerization or development of enantiomeric excess was observed for the branched product under the catalytic conditions, in a cross-over experiment, or under conditions designed to mimic the end of the reaction (Table 2.2).

Table 2.3. Effect of chromium Lewis acid on rate of C—H cleavage



Entry	Additive	Yield[a] t=0.5 hr	t=1.5 hr	t=2.5 hr	k_{rel}
1	-	38	58	84	1.00
2	*R,R*-19 (1 equiv)	42	70	90	1.05

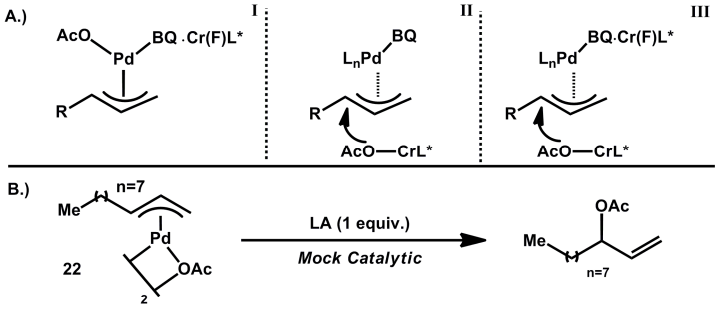
[a]Yields were determined by ^{1}H NMR as compared to an internal standard after being trapped as the π -allyl-Pd chloride dimer and are relative to palladium

I next investigated the role of Salen-Cr^{III}-F (**19)** independently in each of the product forming steps of the catalytic cycle (*i.e.* C—H cleavage and C—O bond formation). A stoichiometric study with undecene and Pd^{II}/bis-sulfoxide catalyst **13** indicates that the rate of C—H cleavage to form [π-allyl-PdOAc]$_2$ (**22**), quantified by trapping as the more stable chloride dimer (**23**), is unaffected by **19** (Table 2.3). To test the effect of **19** on functionalization, reductive elimination from synthetic [π-allyl-PdOAc]$_2$ (**22)** was evaluated with respect to rates and selectivities under conditions that mimic the reaction of a monomeric π-allyl-Pd intermediate during one catalytic reaction cycle (Table 2.4B). As hypothesized, the addition of Lewis acid co-catalyst Salen-Cr^{III}-F (**19)** led to a 10-fold increase in the rate of functionalization relative to identical conditions lacking **19** (Table 2.4B, entries 1 and 2). Moreover, branched allylic acetate product was furnished with comparable enantio- and regioselectivities to that obtained under catalytic conditions. As noted above, functionalization does not occur with **19** in the absence of BQ (Table 2.4B, entry 3).

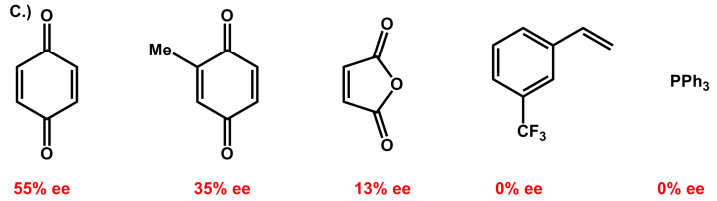
I next turned my attention to evaluating the possible roles of the Lewis acid co-catalyst in the C—O bond forming step. Since the catalytic reaction did not work with sterically hindered π-acids, a quinone was assumed to be a necessary component of any functionalization hypothesis. I envisioned three probable mechanistic scenarios for effecting the observed asymmetric induction during functionalization: (**I**) Salen-Cr^{III}-F (**19)** coordination to BQ to promote and control facial selectivity in the reductive elimination of acetate from a π-allyl-Pd(BQ)OAc intermediate, (**II**) Salen-Cr^{III}-OAc (**20)** delivery of acetate to a π-allyl-Pd(BQ)L intermediate, (**III**) Salen-Cr^{III}-F

(**19)** activation of a π-allyl-Pd(BQ) intermediate with concurrent Salen-Cr^{III}-OAc (**20)** delivery of acetate (Table 2.4A).49[55]

Table 2.4. Effect of chromium Lewis acid on rate of C—O functionalization



Entry	LA	k_{rel}[a]	%Yield[b]	B:L	ee[c]
1	-	1.0	20	>20:1	-
2	(R,R)-19	9.7	85	5.2:1	55
3[d]	(R,R)-19	-	0	-	-
4	(R,R)-20	3.8	41	2.2:1	29
5[e]	(R,R)-20 + TBAF	11.6	96	2.4:1	17
6[e,f]	(R,R)-20 + TBAF	10.7	84	3.0:1	13



A.) Proposed modes of action for chromium lewis acid: **I** Reductive elimination of acetate by a Cr(BQ) activated π-allyl-Pd **II** Delivery from Cr(OAc) to a π-allyl-Pd **III** Delivery from Cr(OAc) to an activated Cr(BQ)-π-allyl-Pd **B.)** Effects of catalysts **19** and **20** on functionalization of a Pd-π-allyl. ***Mock Catalytic*** = 0.2M EtOAc, 11 equiv. AcOH, 20 equiv. BQ, rt, (molarity and equivalents are relative to Pd) [a]rate and selectivity determined by GC, comparison to a standard curve using NB as an internal standard [b]GC yield at 40 min. [c]Determined via GC on β-Cyclodextrin column [d]no BQ added [e]1equiv. *R,R*-**20** and 1 equiv. TBAF·$3H_2O$ added [f]run in THF with π-allyl-Pd-PF_6 as the starting material **C.)** Enantioselectivity trends for functionalization with a variety of π-acids and *R,R*-**19**

In order to evaluate mechanistic scenario **II** that invokes counterion exchange under the reaction conditions to give (Salen)Cr^{III}OAc **20** (Table 2.4A), I independently synthesized **20** and examined its reactivity under both catalytic and stoichiometric conditions. Conversion, enantio-, and regioselectivity are significantly diminished with **20** relative to **19** in both the catalytic and stoichiometric reactions (Table 2.1, entry 15 vs. entry 19, Table 2.4B, entry 4 vs. entry 2). I also evaluated the possibility of a counterion exchange between (*R,R*)-**19** and Pd(OAc)L_n to generate a Pd(F)L_n intermediate and (*R,R*)-**20**. Soluble fluoride (2 equiv., *n*-Bu_4NF) was added to reactions with (*R,R*)-**20** and [π-allyl-PdOAc]$_2$ (**22**) and a marked increase in functionalization was observed. However, the regio- and enantioselectivities of the reaction were inferior to that observed catalytically or stoichiometrically with *R,R*-**19**

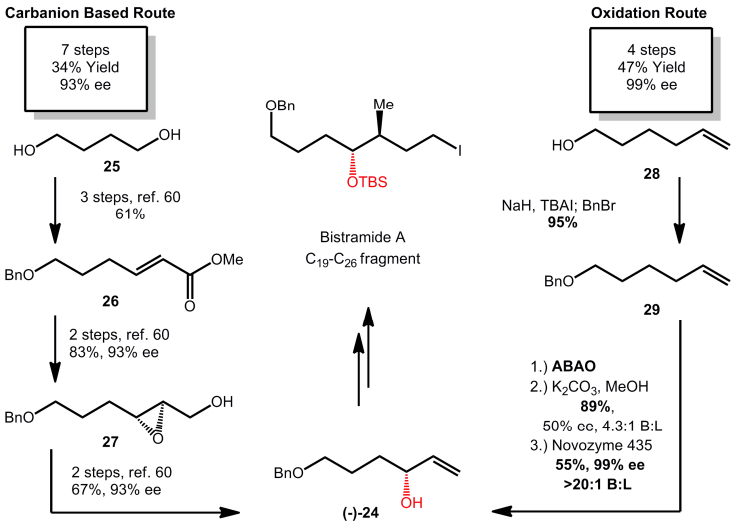
(Table 2.4B, entry 5 vs. entry 2). I also evaluated this hypothesis with (*R,R*)-**20** under conditions known to generate π-allyl-Pd-F (π-allylPd(PF_6)/Bu_4NF)[56] and again noted a dramatic increase in functionalization rate with out a corresponding boost to enantioselectivity. Furthermore, enantioselectivity was observed only with π-acids containing carbonyl groups capable of acting as Lewis basic sites for interacting with **19** (Table 2.4C). Collectively, these results are inconsistent with asymmetric induction arising exclusively through acetate delivery by **20** (Table 2.4A, **II**), and most consistent with **19**·BQ promoted functionalization (Table 2.4A, **I**). However, at this time we cannot rule out a dual activation mechanism in which **20** delivers acetate nucleophile to a π-allyl-Pd(BQ·**19)** electrophilic intermediate (Table 2.4A, **III**).

2.2.3 Application of Asymmetric Branched Allylic Oxidation to Small Molecule Synthesis

While the asymmetric C—H oxidation reaction developed was not synthetically practical due to moderate enantioselectivities, I sought to examine its potential for making chiral allylic alcohol building blocks through its combination with other enantioselective transformations. Allylic alcohols such as those generated by the asymmetric branched allylic C—H oxidation (ABAO) are prevalent in the synthetic literature, in part due to the ease with which they can be further elaborated. These structures are particularly useful in synthetic sequences in which the oxygen atom is remote from other functional groups, making its installation through traditional approaches of stereochemical relay impractical. At present, there are several methods commonly employed to obtain these chiral allylic alcohols.[57,58] In general, a preoxidized starting material is elaborated toward the target through carbanion-based reactions that build up the carbon skeleton. For example, these allylic alcohols can be accessed directly by the addition of a vinyl carbanion to an aldehyde. Unfortunately, stereoselective addition of the vinyl anion remains challenging with high enantioselectivities for this transformation limited to aryl aldehydes.[60a-e] Frequently, a *de novo* route to these allylic alcohols proceeding through a lengthy sequence of functional group manipulations and utilizing a Sharpless asymmetric epoxidation (SAE) to install the key stereocenter is employed.[60f-g] Most often, however, these products are obtained through a kinetic resolution of the racemic alcohol.[60h-i] I hypothesized that combining the ABAO with other enantioselective reactions would afford a more direct, efficient route to these allylic alcohols by avoiding many of the functional group manipulations of traditional carbanion based approaches.[59] Additionally, the significant enantioenrichment afforded by the ABAO should lead to higher yields for any subsequent resolution step as compared to racemic approaches.

I began to explore the practicality of generating chiral allylic alcohols through a C—H activation approach by targeting a prototypical *bis*-oxygenated chiral building block **(-)-24**, a precursor to the C19 – C26 fragment of the potential cancer therapeutic Bistramide A (Scheme 2.4).[60] In the traditional carbanion based route, diol **25** is selectively protected at one terminus, then oxidized and subjected to a Horner-Wadsworth-Emmons olefination at the other to generate ester **26**. After reduction of the ester, SAE affords the epoxy alcohol **27** in 93% ee. The primary alcohol is then converted to a halogen, which is eliminated with zinc to afford the desired allylic alcohol **(-)-24** in a total of 7 steps and 34% overall yield.

Scheme 2.4. C—H oxidation vs. carbanion based route for the synthesis of (-)-**24**

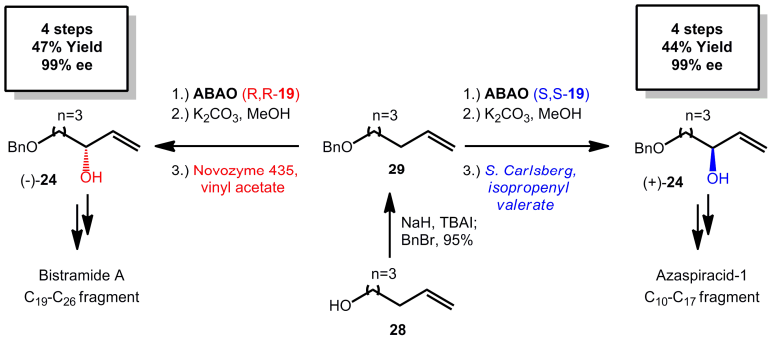


Alternatively, after simple protection of commercially available **28**, allylic oxidation installs the oxygen functionality directly at the desired oxidation state, with significant enrichment toward the desired enantiomer (50% ee). Subsequent methanolysis and enzymatic resolution gives enantiopure **(-)-24** in a total of 4 steps and 47% overall yield. The C—H oxidation route reduces the overall step count and improves the yield by minimizing functional group manipulations and unnecessary oxidation state changes. Furthermore, I found that enzymatic acylation not only increases the enantioselectivity of the reaction, but also rapidly acylates the minor linear allylic alcohol, making purification of the final product trivial.

Broad use of an enantioselective transformation requires that either enantiomer of the desired product can be obtained with high enantioselectivity. Fortunately, catalyst **19** is readily available as either enantiomer, and careful enzyme selection allows for enrichment of each stereoisomer of the product.[61] To demonstrate this, I used *S,S*-**19** and a protease resolution to generate **(+)-24** in 99% ee and nearly identical overall yield to the route

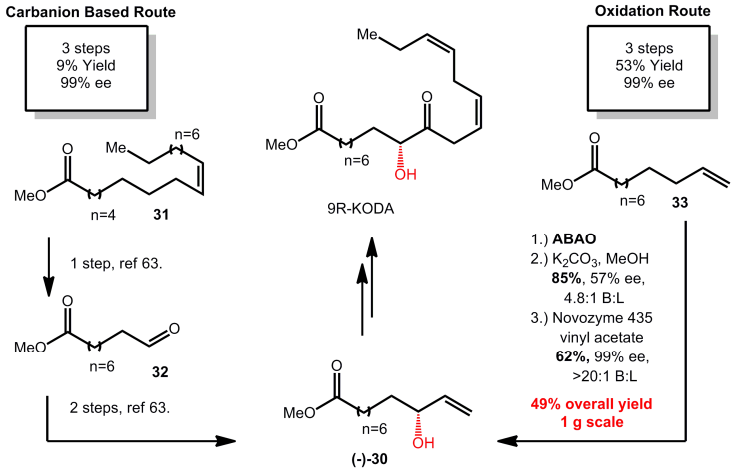
previously described for **(-)-24** (Scheme 2.5). This matches the flexibility of the traditional *de novo* approach to these compounds which was utilized to make **(+)-24** in a total synthesis of the potent biotoxin Azaspiracid A.[62]

Scheme 2.5. C—H oxidation approach to either enantiomer of allylic alcohol **24**



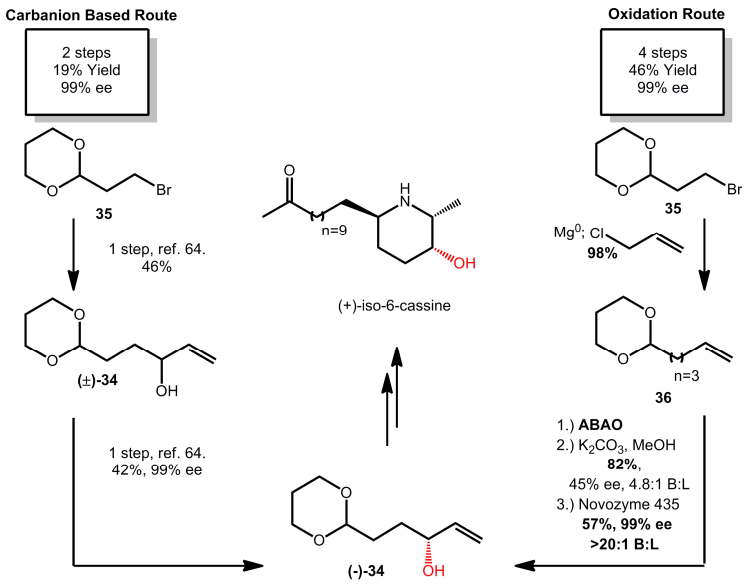
I next sought to compare the C—H oxidation route to chiral allylic alcohols to traditional resolution strategies. Ester **(-)-30** was synthesized *en route* to the flower inducing factor 9R-KODA (Scheme 2.6).[63] In order to avoid a lengthy sequence of FGMs, the original researchers chose to ozonolize methyl oleate (**31**) and attempt to vinylate the resultant aldehyde in the presence of an ester group. While the authors observed a significant diminishment in overall yield, they were able to quickly access (±)-**30**. Subsequent enzymatic kinetic resolution afforded enantiopure **(-)-30** in three steps, though the poor chemoselectivity of the vinylation step lead to an overall yield of only 9%. Conversely, ABAO of commercially available α-olefin **33** followed by methanolysis and resolution yielded **(-)-30** in equivalent step count and enantiopurity, but with a 6-fold increase in total yield (3 steps, 53% yield, 99%ee). Importantly, this reaction sequence was run on gram scale with no diminishment in yield.

Scheme 2.6. C—H oxidation vs. carbanion based route for the synthesis of ester (-)-**30**



Due to the large number of commercially available α-olefin starting materials, the C—H oxidation sequences presented thus far have begun with fully constructed carbon frameworks. However, I sought to find an example in which no such olefin was available, and test whether a C—H oxidation route was still competitive with traditional approaches. Synthesis of allylic alcohol **(-)-34** began from a commercially available, protected starting material (Scheme 2.7).[64] Formation of a Grignard reagent from bromide **35** followed by its addition into acrolein gave racemic alcohol (±)-**34** in one step. Again, this addition proceeds with poor chemoselectivity, giving a mixture of 1,2- and 1,4-addition products. Enzymatic resolution then yielded the desired **(-)-34** in two steps and 19% overall yield. From the same commercially available bromide **35**, a suitable starting material for C—H oxidation (**36**) can be obtained by simple allylation, a C—C bond forming reaction with no chemoselectivity issues. Subjecting the resultant olefin to the C—H oxidation, methanolysis, enzymatic resolution sequence affords the desired enantiopure alcohol **(-)-34** in four steps and 46% overall yield, doubling the yield of the traditional route for a substrate requiring no FGMs to prepare and further illustrating the promise this strategy has for generating these chiral building blocks.. This is enabled by the ease of installing the allyl moiety and the mild and selective nature of this C—H oxidation.

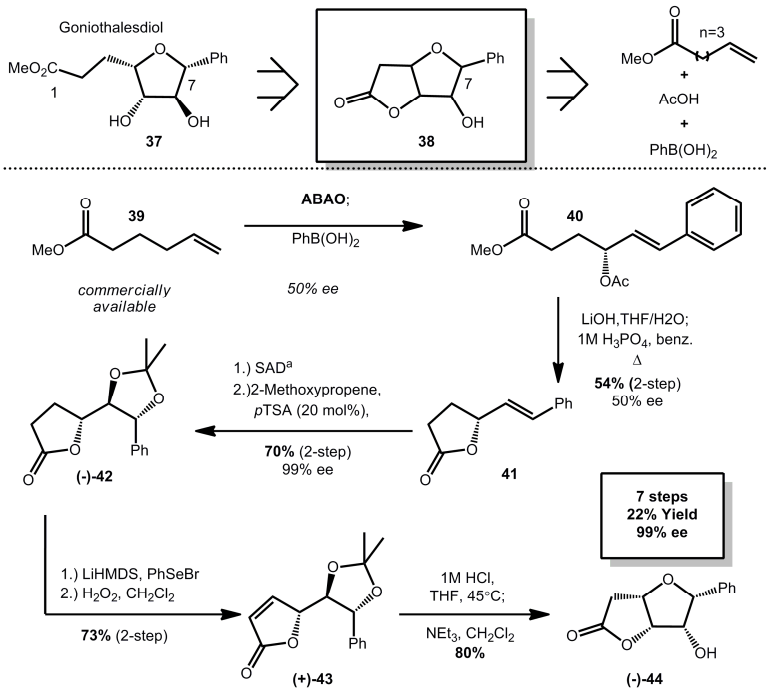
Scheme 2.7. C—H oxidation vs. carbanion based route for the synthesis of (-)-**34**



I have demonstrated how the ABAO can be combined with enzymatic resolution to afford enantiopure allylic alcohols rapidly and in good yield. However, reagent controlled enantioselective transformations can also be used to enrich C—H oxidation products by generating separable diastereomers. I sought to exemplify this idea through a synthesis of the densely functionalized furan core of Goniothalesdiol. Due to its potent activity against

mouse leukemia cells, a number of total syntheses of Goniothalesdiol (**37**) and its epimers have been undertaken.[65] Generally these routes begin with chiral pool materials, and are therefore limited in the derivatives of **37** they can rapidly access. One approach initially developed by Gracza and co-workers to **37** proceeds through the tetrasubstituted furan core **38**.[65b] I recognized that an ABAO tandem oxidative Heck sequence could access this core structure rapidly (Scheme 2.8).[42d] Subsequent Sharpless asymmetric dihydroxylation (SAD) would generate separable diastereomers, allowing us to obtain enantiopure material for further reaction. Significantly, our *de novo* approach to **38** is quite flexible, allowing us to selectively control the stereochemistry at the 5, 6, and 7 positions of the core furan as well as easily vary the nature of the aryl substituent at position 7. While previous syntheses have relied primarily on C—C bond forming reactions, this plan involves a steady increase in complexity through hydrocarbon oxidations.

Scheme 2.8. Enantioselective C—H oxidation approach to the core furan the Goniothalesdiol family



[a]SAD = Sharpless asymmetric dihydroxylation. See experimental section for details

I decided upon furan core **(-)-44** as an interesting target for this strategy because, to the best of my knowledge, 6-*epi*-Goniothalesdiol has yet be synthesized or evaluated medicinally. My route began with the ABAO of methyl ester **39**, followed by the addition of phenyl boronic acid. Gratifyingly, the ABAO/oxidative Heck reaction furnished ester **40** in a one pot transformation. Hydrolysis and cyclization of the crude material gave lactone **41** in 54% yield over two steps. SAD of this material and subsequent ketal protection of the resultant diol,

gave 70% of diastereomerically and enantiomerically pure **(-)-42**. The relative and absolute stereochemistry of this compound were determined by X-ray crystallographic analysis of *para*-Bromophenyl **(-)-42**. This derivative was rapidly generated simply by switching to 4-bromophenylboronic acid in the ABAO/oxidative Heck step, highlighting the ease of modifying the core furan through this route. Selenation/dehydroselenation of lactone **(-)-42** afforded unsaturated γ-lactone **(+)-43** in 73% yield. Deprotection of the acetonide followed by *in situ* NEt_3 assisted cyclization afforded the desired tetrasubstituted furan **(-)-44** in 7 total steps and 22% overall yield. Previous C—C bond forming routes to this core structure proceeded in 8[68b] and 10[68d] steps with 6% and 9% overall yields respectively. This case study demonstrates the potential of hydrocarbon oxidations for synthesizing densely functionalized fragments, and exemplifies the flexibility of this synthetic approach for generating derivatives.

2.3 Conclusions

In conclusion, I discovered a heterobimetallic Pd^{II}bis-sulfoxide/(Salen)$Cr^{III}F$ system for asymmetric allylic C—H oxidation of terminal olefins that proceeds with the highest levels of enantioselectivity for this olefin class to date.[66] To the best of our knowledge, this represents the first demonstration of a chiral Lewis acid co-catalyst interacting with an organometallic intermediate to influence the stereochemical course of a catalytic process. Moreover, Lewis acids are proving to be a general means for promoting reactivity under the acidic, electrophilic reaction conditions necessary for C—H activation with catalyst **13**. I have also established that the asymmetric branched allylic oxidation reaction can be combined with other enantioselective transformations to afford enantiopure, polyoxygenated allylic alcohols rapidly and in good yields. The C—H oxidation approach is complimentary to commonly used resolution and *de novo* synthetic strategies that require significant numbers of protection/deprotection steps and functional group manipulations. Due to the ease and efficiency of this approach, I expect that this strategy will find widespread use for the synthesis of these commonly used intermediates.

2.4 Experimental Section

General Information: All commercially obtained reagents were used as received; $Pd(OAc)_2$, (Strem Chemicals), (1R,2R)-(-)-[1,2-Cyclohexanediamino-N,N'-bis(3,5-di-t-butylsalicylidene)]Chromium(III)Cl, (1S,2S)-(+)-[1,2-Cyclohexanediamino-N,N'-bis(3,5-di-t-butylsalicylidene)]Chromium(III)Cl, Benzoquinone (Aldrich), undecene (Fluka), acetic acid (Fisher) . $Pd(OAc)_2$ was stored in a glove box under an argon atmosphere and weighed out in

the air prior to use. Commercially available "White Catalyst" (1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate) from Aldrich was found to be equivalent to that prepared freshly by the published procedure.[67] Solvents 1,4-dioxane, diethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). *Tert*-butylmethyl ether (TBME), ethyl acetate (EtOAc), and acetonitrile (Sure/Seal) were obtained from Sigma-Aldrich and used as received. All allylic oxidation reactions were run under air. Achiral gas chromatographic (GC) analyses were performed on Agilent Technologies 6890N Series instrument equipped with FID detectors using a HP-5 (5%-Phenyl)-methylpolysiloxane column (30m, 0.32mm, 0.25μm). Chiral gas chromatographic (GC) analyses were performed on an Agilent Technologies 5890A Series instrument equipped with an FID detector using a J&W Scientific β-cyclodextrin column (30m, 0.25mm, 0.25μm). HPLC analysis was performed on an Agilent Technologies 1100 HPLC system with a model 1100 Quaternary Pump, Diode Array Detector, Thermostat, and Autosampler. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, potassium permanganate, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still et al.[68] using EM reagent silica gel 60 (230-400 mesh). ^{1}H NMR spectra were recorded on a Varian Unity 400 (400 MHz) or a Varian Unity 500 (500 MHz), or a Varian Unity Inova 500NB spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C- NMR spectra were recorded on a Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory.

(1R,2R)-(-)-[1,2-Cyclohexanediamino-N,N'-bis(3,5-di-t-butylsalicylidene)]Chromium (III) Acetate (20)[69]
Commercially available (1R,2R)-(-)-[1,2-Cyclohexanediamino-N,N'-bis(3,5-di-t-butylsalicylidene)]Chromium(III) Chloride (0.500 g, 0.78 mmol) was added to a scintillation vial wrapped in aluminum foil. To this was added *tert*-butylmethyl ether (TBME) (7.8 mL) followed by silver(I) acetate (0.126 g, 0.78 mmol). The reaction was capped and stirred vigorously for 7 hrs, at which time the liquids were filtered through Celite©, rinsing with TBME (~25 mL). The solvent was removed *in vacuo* and the catalyst was used without further purification. **IR**: 2961, 2910,

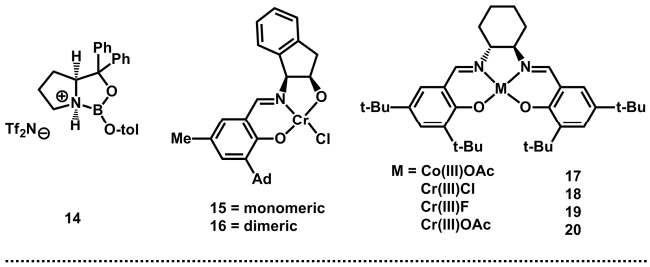
2869, 1621, 1537, 1435, 1361, 1320, 1255, 1201, 1170, 1132, 1099, 1076, 1028, 837, 746 **HRMS**: (FAB) m/z calculated for $C_{36}H_{52}O_2N_2Cr$ $[M + - OAc]^+$: 596.3434; found: 596.3435.

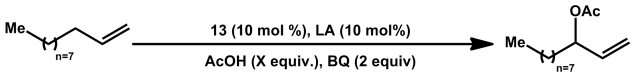
General Procedure for Asymmetric Branched Allylic Oxidation (Table 2.1): A vial (8 mL borosilicate) was charged with the following: 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate(**13**) (10 mol%, 0.10 mmol, 50 mg); (1R,2R)-(-)-[1,2-Cyclohexanediamino-N,N'-bis(3,5-di-t-butylsalicylidene)]Chromium(III)F(*R,R*-**19**) (10 mol%, 0.10 mmol, 61.6 mg), 1,4-benzoquinone (2 equiv., 2.0 mmol, 216 mg), an activated 4Å MS bead (~30 mg), and a Teflon© stir bar. A separate vial (2 mL, borosilicate) was charged with the following: substrate (1.0 mmol), AcOH (1.1 equiv., 63 μL), and EtOAc (200 μL). The liquids were transferred to the solids via pipette and the vial rinsed with EtOAc (3 x 100 μL). After carefully stirring for 48 hrs at room temperature, the reaction mixture was transferred to a separatory funnel with ~3 mL EtOAc and then diluted with hexanes (200 mL). The organic layer was rinsed with sat. aq. $NaHSO_3$ (1 x 50 mL) and 5% aq. K_2CO_3 (2 x 50 mL). *Caution should be taken when combining aqueous layers as carbon dioxide is evolved.* The combined aqueous layers were back extracted with hexanes (100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and reduced *in vacuo.* The resulting oil was re-dissolved in hexanes (50 mL) and extracted again with 5% aq. K_2CO_3 (3 x 10 mL) to remove residual hydroquinone. The organic layer was again dried ($MgSO_4$), filtered, and reduced *in vacuo* to afford a clean mixture of allylic oxidation products and any unreacted starting material from which the conversion, yield, and B:L ratio were determined (^{1}H NMR). Enantioselectivities were determined by chiral GC using a β-cyclodextrin column (see individual substrates for details).

General Procedure for Screens (Table 2.1, Table 2.2, Table 2.3): Vials (2 mL or 4 mL borosilicate) were charged with the following solids: 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (**13**) (10 mol%); Lewis acid (10 mol%), and oxidant (2 equiv.). Separate vials (2 mL, borosilicate) were charged with the following: 1-undecene (0.1 mmol or 0.2 mmol), nitrobenzene (internal GC standard, 40 mol %), AcOH, and solvent. Aliquots were taken from the liquid vials (~10 μL filtered with Et_2O through a short pipette plug of silica), to determine GC initial ratios of 1-undecene to nitrobenzene. The liquids were transferred *via* pipette into the appropriate solids vial, charged with a stir bar, capped and allowed to stir at room temperature or 45°C. Aliquots were taken at time intervals to determine GC yields. Response factors relative to undecene were determined for the branched and linear allylic acetates. Catalyst **13** was prepared as previously described.[67] Commercially available **13** (Aldrich) was found to give comparable yields and selectivities. Lewis acid **14** was prepared as described[70] and added as a solution in

CH_2Cl_2. Lewis acid's **15** and **16** were prepared as previously described.[71,72] Lewis acid **17** was prepared from commercially available (1R,2R)-(-)-[1,2-Cyclohexanediamino-N,N'-bis(3,5-di-t-butylsalicylidene)]Cobalt (II) as previously described.[73,74] Lewis acid **19** was prepared from commercially available (1R,2R)-(-)-[1,2-Cyclohexanediamino-N,N'-bis(3,5-di-t-butylsalicylidene)]Chromium(III) Chloride as previously described.[75]

Table 2.5. Analysis of Lewis acid mediated enantioselective C—H bond oxidation





Entry	LA	M	X	T	% Yield [a]	B:L	ee [b]
1	-	0.33	4	45	71	>30:1	0
2	14	0.33	4	45	27	28:1	0
3	15	0.33	4	45	7	8:1	0
4	16	0.33	4	45	41	6:1	0
5	17	0.33	4	45	6	>30:1	0
6 [c]	17	2	1.1	rt	1	1.9:1	4
7 [d]	17	2	1.1	rt	4	2.8:1	14
8	18	0.33	4	45	7	1.2:1	32
9	18	0.33	1.1	45	10	1.2:1	32
10	18	2	1.1	rt	35	1.1:1	32
11 [d]	18	2	1.1	rt	41	1.4:1	32
12	19	0.33	4	45	74	9.3:1	9
13	19	0.33	1.1	45	59	7.9:1	15
14	19	2	1.1	rt	86	4.6:1	54
15 [d]	19	2	1.1	rt	93	5.1:1	57
16	20	0.33	4	45	11	3.2:1	8
17	20	0.33	1.1	45	8	2.0:1	14
18	20	2	1.1	rt	50	1.5:1	29
19 [d]	20	2	1.1	rt	71	2.0:1	31

[a]GC yield, average of at least two runs [b]Determined by Chiral GC [c]TBME, 1.1 equiv. DIPEA [d]EtOAc solvent, 4Å MS bead added(~30 mg), 48 hrs.

Table 2.5. *Solids vial* (2 mL borosilicate): 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (**13**) (0.02 mmol, 10.0 mg)(Entries 1-19), benzoquinone (2 equiv., 0.4 mmol, 43 mg)(Entries 1-19), **14** (0.02 mmol, 0.1 M solution in CH_2Cl_2, 200 µL)(Entry 2), **15** (0.01 mmol, 9.9 mg)(Entry 3), **16** (0.02 mmol, 9.7 mg)(Entry 4), **17** (0.02 mmol, 13.2 mg)(Entry 5-7), **18** (0.02 mmol, 12.6 mg)(Entries 8-11), **19** (0.02 mmol, 12.3 mg)(Entries 12-15), **20** (0.02 mmol, 13.2 mg)(Entry 16-19). *Liquids vial* (2 mL borosilicate): AcOH (4 equiv., 0.8 mmol, 48 mg, 46 µL)(Entries 1-5, 8, 12, 16), AcOH (1.1 equiv., 0.22 mmol, 13 mg, 12.6 µL)(Entries 6-7, 9-11, 13-15, 17-19), 1-undecene (1 equiv., 0.2

mmol, 31 mg, 41 μL)(Entries 1-19), nitrobenzene (internal GC standard, 0.08 mmol, 9.4 mg, 8.6 μL)(Entries 1-19), 0.606 mL dioxane (Entries 1-5, 8-9, 12-13, 16-17), 100 μL dioxane (Entries 10, 14, 18), 100 μL TBME (Entry 6), Diisopropylethylamine (1.1 equiv., 0.22 mmol, 28.4 mg, 39 μL) (Entry 6), 100 μL EtOAc (Entries 7, 11, 15, 19), 45^{o}C (Entries 1-5, 8-9, 12-13, 16-17), room temperature (Entries 6-7, 10-11, 14-15, 18-19). Results are reported as an average of two to three runs, with yields and selectivities determined by GC.

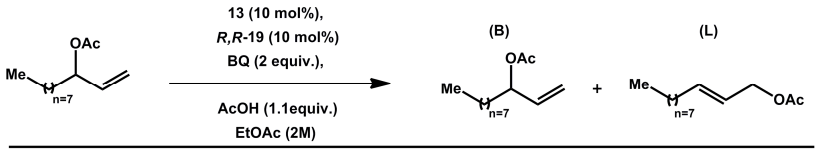
Mechanistic Explorations

Relative Rates of π-σ- π Isomerization and Functionalization

(*Z*)-1-deuterio-1-decene was prepared by *n*-BuLi deprotonation of decyne quenched with D_2O,[76] followed by hydrozirconation of 1-deuterio-1-decyne quenched with H_2O.[77] This material was then submitted to the standard branched allylic oxidation conditions[42b] (Table 2.1, entry 15) and the double bond geometry of the product evaluated after reaction. ^{1}H NMR showed a 1:1 ratio of *cis*- and *trans*-3-acetoxy-1-deuterio-1-decene. ^{1}H NMR spectra of the starting material and crude product mixture are included in Appendix B.

Evaluation of Potential LA Mediated Asymmetric Allylic Rearrangement

Table 2.6. Mechanistic evaluation of LA as an agent for enantioselective allylic acetate rearrangement



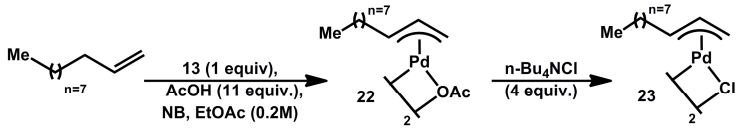
Entry	Modifications	t=0 B:L	t=24 B:L	t=24 %ee
1	-	>99:1	96:4	0
2	0.5 equiv. allylcyclohexane	>99:1	>99:1	0
3	0.5 equiv. allylcyclohexane BQ (1 equiv.). DHQ (1 equiv.) AcOH (0.1 equiv.)	>99:1	>99:1	0
4	no Pd	>99:1	>99:1	0
5	no 13	>99:1	98:2	0

Table 2.6. Authentic 3-acetoxy-1-undecene made through our standard allylic oxidation conditions was re-exposed to the optimized reaction conditions (Table 1, Entry 6) for 24 hours and no appreciable change in B:L or % ee was observed (Table S2, Entry 1). Similarly, we were unable to effect this transformation in the presence of another terminal olefin in a crossover experiment (Table S2, Entry 2). Mimicking conditions of the reaction after significant conversion also failed to effect asymmetric isomerization (Table S2, Entry 3). *Solids vial* (2 mL borosilicate): 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (**13**) (0.01 mmol, 5.0 mg)(Entries 1-3, 5), benzoquinone (2 equiv.,

0.2 mmol, 21.7 mg)(Entries 1-2, 4-5), benzoquinone (1 equiv., 0.1 mmol, 10.9 mg)(Entry 3), hydroquinone (1 equiv., 0.1 mmol, 11.0 mg) *R,R*-**19** (0.01 mmol, 6.2 mg)(Entries 1-4). *Liquids vial* (2 mL borosilicate): AcOH (1.1 equiv., 0.11 mmol, 6.6 mg, 6.3 µL)(Entries 1-2, 4-5),AcOH (0.01 equiv., 0.01 mmol, 0.6 mg, 0.6 µL)(Entry 3), 3-acetoxy-1-undecene (1 equiv., 0.1 mmol, 21 mg (Entries 1-5), allylcyclohexane (0.5 equiv., 0.05 mmol, 12.4 mg)(Entries 2-3), nitrobenzene (internal GC standard, 0.04 mmol, 4.7 mg, 4.1 µL)(Entries 1-5), 50 µL EtOAc (Entries 1-5), room temperature (Entries 1-5). Results are reported as an average of two to three runs, with yields and selectivities determined by GC.

Effect of Chromium Lewis Acid R, R-19 on C—H Cleavage

Table 2.7. Effect of chromium Lewis acid **19** on rate of C—H cleavage



Entry	Additive	Yield[a] t=0.5 hr	t=1.5 hr	t=2.5 hr	k_{rel}
1	-	38	58	84	1.00
2	*R,R*-19 (1 equiv)	42	70	90	1.05

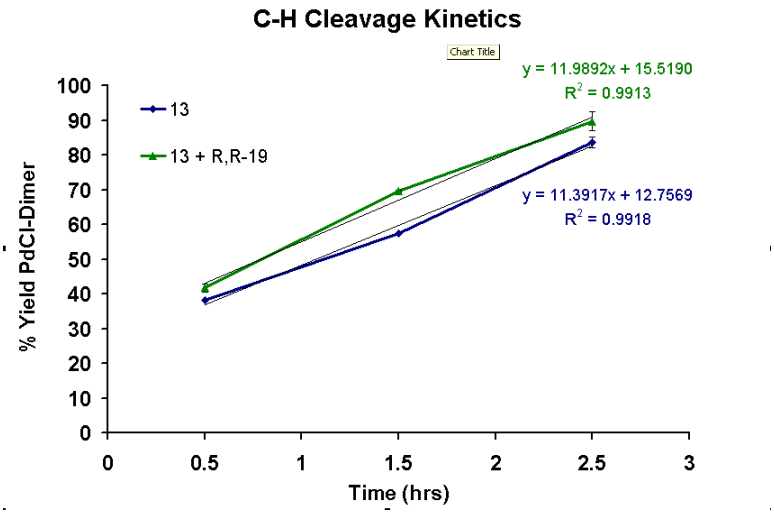
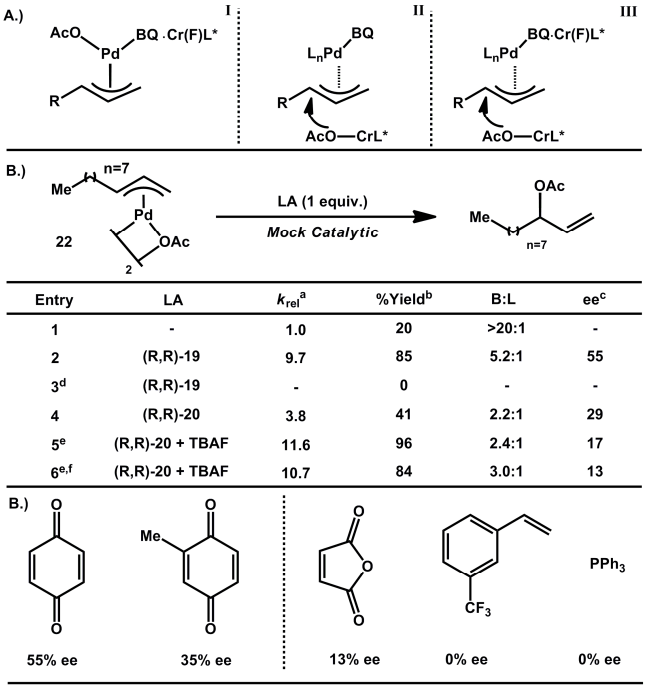


Table 2.7. Vial (2 mL borosilicate): 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (**13**) (0.02 mmol, 10.0 mg)(Entries 1-3), *R,R*-**19** (0.02 mmol, 12.6 mg) (Entry 3),and a Teflon© stir bar. A stock solution of 1-undecene (84 µL, 0.4 mmol) and EtOAc (2 mL) was prepared. Directly to the solids was added via syringe 104 µL of this stock solution (0.02 mmol 1-undecene), followed by AcOH (12.6 µL, 0.22 mmol). Both vials were carefully stirred at room temperature. After the indicated time, *n*-Bu_4NCl (0.08 mmol, 22.2 mg) was added, and the mixture allowed to stir an additional 1 hr at room temperature. The contents of each vial were then transferred to a 7 cm pipette plug

of silica gel. 2 mL of $CDCl_3$ was used to rinse the Pd-chloride dimer through the silica into a 25 mL recovery flask. The solvent was removed *in vacuo*. A stock solution of nitrobenzene (10 uL, 0.09 mmol) and $CDCl_3$ (10 mL) was prepared. 1.5 mL of this stock was added to each flask, the flasks were capped, vortexed for 15 seconds, and a 0.7 mL aliquot was removed via syringe from each and transferred to a separate NMR tube. Results are reported as an average of at least three runs, with yields determined by ^{1}H NMR as compared to the internal standard and error bars indicating standard deviation from the mean. Relative rates are based on the slope of a linear fit to the observed data for an experimental condition (Entry X) divided by that of the control (Entry 1).

Effect of Chromium Lewis Acids *R, R*-19 and *R, R*-20 on Functionalization of π-allyl-Pd-OAc

Table 2.8. Effect of chromium Lewis acid on rate of C—O functionalization



Entry	LA	k_{rel}[a]	%Yield[b]	B:L	ee[c]
1	-	1.0	20	>20:1	-
2	(R,R)-19	9.7	85	5.2:1	55
3[d]	(R,R)-19	-	0	-	-
4	(R,R)-20	3.8	41	2.2:1	29
5[e]	(R,R)-20 + TBAF	11.6	96	2.4:1	17
6[e,f]	(R,R)-20 + TBAF	10.7	84	3.0:1	13

A.) Proposed modes of action for chromium lewis acid: **I** Reductive elimination of acetate by a Cr(BQ) activated Pd-p-allyl **II** Delivery from Cr(OAc) to a Pd-p-allyl **III** Delivery from Cr(OAc) to an activated Cr(BQ)-Pd-p-allyl **B.)** Effects of catalysts 3 and 4 on functionalization of a Pd-p-allyl. ***Mock Catalytic*** = 0.2M EtOAc, 11 equiv. AcOH, 20 equiv. BQ, rt, (molarity and equivalents are relative to Pd) [a]rate and selectivity determined by GC, comparison to a standard curve using NB as an internal standard [b]GC yield at 40 min. [c]Determined via GC on β-Cyclodextrin column [d]no BQ added [e]1equiv. *R,R*-**20** and 1 equiv. TBAF·3H_2O added [f]run in THF with π-allyl-Pd-PF_6 as the starting material **C.)** Enantioselectivity trends for functionalization with a variety of π-acids and *R,R*-**19**

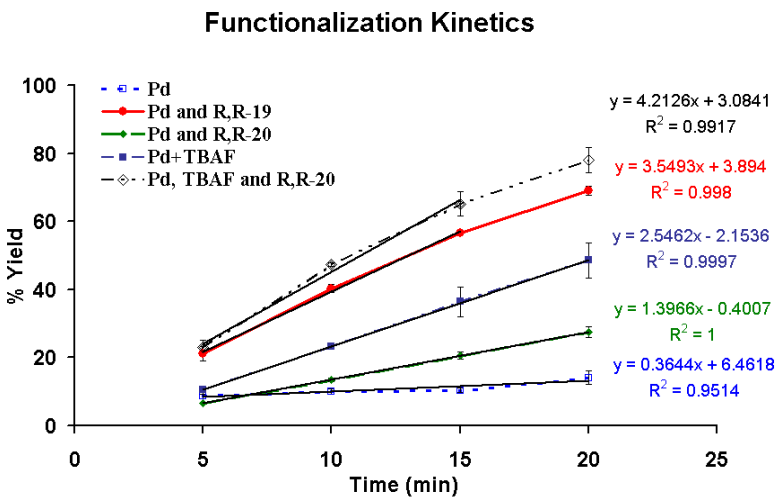
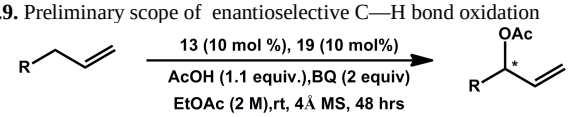
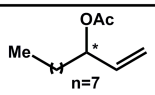
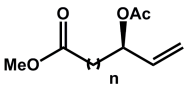
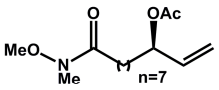
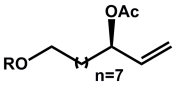
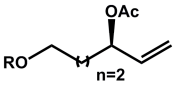
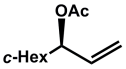


Table 2.8. Vial (2 mL borosilicate): bis[acetato(1,2,3-*trihapto*-1-undecene)palladium (II)] **22**[78] (0.011 mmol, 7.0 mg)(Entries 1-5), Hexafluorophospho(1,2,3-*trihapto*-1-undecene)palladium (II)[79] (0.011 mmol)(Entry 6),1,4-benzoquinone (0.22 mmol, 23.8 mg)(Entries 1-3, 5-6), *R,R*-**19** (0.022 mmol, 13.5 mg) (Entries 2-3), *R,R*-**20** (0.022 mmol, 14.4 mg) (Entry 4-6), tetrabutylammonium fluoride trihydrate (0.022 mmol, 6.9 mg)(Entries 5-6), and a Teflon© stir bar. A stock solution of nitrobenzene (36 µL, 0.34 mmol) and EtOAc (2 mL) was prepared. (Entries 1-5). A stock solution of nitrobenzene (36 µL, 0.34 mmol) and THF (2 mL) was prepared. (Entry 6). Directly to the solids was added via syringe 111 µL of the stock solution (0.018 mmol nitrobenzene), followed by AcOH (14 µL, 0.24 mmol)(Entries 1-6). Each vial was then capped and stirred at room temperature. At each time point, an aliquot (~7 µL) was removed and passed through a short plug of silica in a pipette into a 2 mL borosilicate vial. Unreacted SM was then quenched with two drops of sat. aq. $NaHSO_3$. Each vial was capped and vortexed for 30 seconds. After allowing the layers to separate, the organic layer was decanted away and passed through a second pipette silica plug into a GC vial. Results are reported as an average of at least three runs, with yields and selectivities determined by GC. Yields were determined by comparison to a calibration curve of authentic 3-acetoxy-1-undecene, synthesized independently, versus nitrobenzene, with error bars indicating the standard deviation from the mean.

Exploration of Functional Group Tolerance and Scope

Table 2.9. Preliminary scope of enantioselective C—H bond oxidation

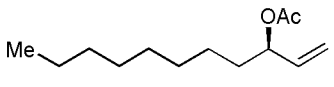


Entry	Product		%Yield[a] (%brsm[b])	B:L	ee[c]
1			92	5.3:1	59
2[d]			92	5.3:1	-59
3		n=7	89	4.8:1	57
4		n=2	69 (73)	4.6:1	50
5			81 (88)	4.4:1	54
6 R=TBDPS			84 (90)	4.4:1	63
7 R=H			83	4.4:1	50
8 R=THP			91	3.6:1	49
9 R=Bn			90	4.3:1	45
10[e]			78 (83)	1.5:1	62

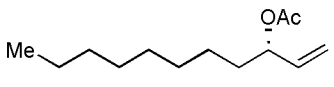
[a]isolated yields of allylic oxidation products (1.0 mmol substrate), average of at least three runs [b]based on recovered starting material [c]determined by chiral GC. See substrate entries below for individual details [d]S,S-**19** [e]72 hrs

General Procedure for Asymmetric Branched Allylic Oxidation (Table 2.9): A vial (8 mL borosilicate) was charged with the following: 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate(**13**) (10 mol%, 0.10 mmol, 50 mg); (1R,2R)-(-)-[1,2-Cyclohexanediamino-N,N'-bis(3,5-di-t-butylsalicylidene)]Chromium(III)F (*R,R*-**19)** (10 mol%, 0.10 mmol, 61.6 mg), 1,4-benzoquinone (2 equiv., 2.0 mmol, 216 mg), an activated 4Å MS bead (~30 mg), and a Teflon© stir bar. A separate vial (2 mL, borosilicate) was charged with the following: substrate (1.0 mmol), AcOH (1.1 equiv., 63 µL), and EtOAc (200 µL). The liquids were transferred to the solids via pipette and the vial rinsed with EtOAc (3 x 100 µL). After carefully stirring for 48 hrs at room temperature, the reaction mixture was transferred to a separatory funnel with ~3 mL EtOAc and diluted with hexanes (200 mL). The organic layer was rinsed with sat. aq. $NaHSO_3$ (1 x 50 mL) and 5% aq. K_2CO_3 (2 x 50 mL). *Caution should be taken when combining aqueous layers as carbon dioxide is evolved.* The combined aqueous layers were back extracted with hexanes (100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and reduced *in vacuo.* The resulting oil was re-dissolved in hexanes (50 mL) and extracted again with 5% aq. K_2CO_3 (3 x 10 mL) to remove residual hydroquinone. The organic layer was again dried ($MgSO_4$), filtered and reduced *in vacuo* to afford a clean mixture of allylic oxidation products and any unreacted starting material from which the B:L, yield, and conversions were determined

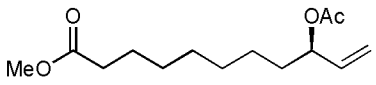
(^{1}H NMR). Reported yields and selectivities are an average of at two to three runs. Enantiomeric excess was determined by chiral GC (β-cyclodextrin column), as compared to racemic standards generated through our standard branched oxidation chemistry.[Error! Bookmark not defined.] Absolute stereochemistry was determined by performing the optimized reaction conditions (Table 1, Entry 6) on 1-octene. The resultant product was compared to acetylated commercially available Matasuka alcohol ((*S*)-1-octen-3-ol, Fluka, >99% ee) and determined to be enriched in the *R* enantiomer when (*R*,*R*)-**19** was used as catalyst. The remaining substrates were assigned by analogy. Slight variations in B:L ratios and ee's were noted based on batch of Cr catalyst. Representative high and low numbers are given for each substrate, and factored into the averages reported in Table 2.5.



Entry 1. Run 1: 201 mg, 0.945 mmol, 95% yield, [B:L] = 5.1:1, [ee] = 60%. Run 2: 190 mg, 0.893 mmol, 89% yield; [B:L] = 5.3:1, [ee] = 58%. Run 3: 197 mg, 0.927 mmol, 93% yield; [B:L] = 5.3:1, [ee] = 60%. (β-cyclodextrin, 110°C isothermal, t_R(major) = 10.43 min., t_R(minor) = 11.02 min.), [**average yield:** 92%]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.77 (ddd, J = 17.2, 10.8, 6.4 Hz, 1H), 5.25-5.14 (m, 3H), 2.06 (s, 3H), 1.66-1.51 (m, 2H), 1.40-1.19 (m, 12H), 0.87 (t, J = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.4, 136.6, 116.5, 74.9, 34.2, 31.8, 29.4, 29.4, 29.2, 25.0, 22.6, 21.3, 14.1; **IR** (neat, cm^{-1}) 3089.1, 2931.0, 2855.8, 1741.9, 1466.2, 1371.0, 1239.6; **HRMS** (ESI) m/z calculated for $C_{13}H_{24}O_2Na$ $[M + Na]^+$: 235.1674; found: 235.1667.

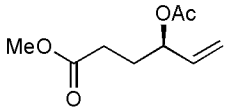


Entry 2. *S*,*S*-**19** used as LA catalyst. [ee] = 59% (β-cyclodextrin, 110°C isothermal, t_R(minor) = 10.43 min., t_R(major) = 11.02 min.)

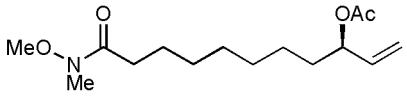


Entry 3. Run 1: 235 mg, 0.915 mmol, 92% yield, [B:L] = 5.2:1, [ee] = 58%. Run 2: 225 mg, 0.879 mmol, 88% yield; [B:L] = 5.1:1, [ee] = 58%, Run 3: 224 mg , 0.876 mmol, 87% yield; [B:L] = 4.0:1, [ee] = 55% (β-cyclodextrin, 130°C isothermal, t_R(major) = 34.30 min., t_R(minor) = 35.49 min.), [**average yield:** 89%]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.78 (ddd, J = 17.1, 10.5, 6.5 Hz, 1H), 5.24-5.14 (m, 3H), 3.66 (s, 3H), 2.29 (t, J = 8.0 Hz, 2H), 2.05 (s, 3H), 1.62-1.53 (m, 4H), 1.29 (bs, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.2, 170.3, 136.5, 116.5, 74.8, 51.4, 34.1, 34.0, 29.1, 29.0, 29.0, 24.9, 24.8, 21.2; **IR**

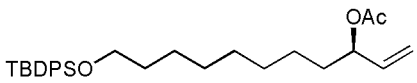
(neat, cm^{-1}) 3089.1, 2932.9, 2858.2, 1742.0, 1436.3, 1371.5; **HRMS** (ESI) m/z calculated for $C_{14}H_{24}O_4Na$ [M + $Na]^+$: 279.1572; found: 279.1564.



Entry 4. Run 1: 132 mg, 0.708 mmol, 71% yield, [B:L] = 4.6:1, [ee] = 50%. Run 2: 119 mg, 0.640 mmol, 64% yield; [B:L] = 4.7:1, [ee] = 49%. Run 3: 131 mg, 0.706 mmol, 71% yield; [B:L] = 4.6:1, [ee] = 50%. (β-cyclodextrin, 110°C isothermal, t_R(major) = 5.52 min., t_R(minor) = 5.83 min.), [**average yield:** 69%, with 4% recovered SM (5.1 mg)]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.76 (ddd, J = 17.3, 10.5, 6.3 Hz, 1H), 5.29-5.18 (m, 3H), 3.68 (s, 3H), 2.36 (t, J = 7.5 Hz, 2H), 2.06 (s, 3H), 2.00-1.93 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.3, 170.1, 135.6, 117.2, 73.6, 51.7, 29.6, 29.1, 21.1; **IR** (neat, cm^{-1}) 3088.0, 2953.7, 2853.7, 1742.2, 1438.3, 1372.7, 1236.7; **HRMS** (ESI) m/z calculated for $C_9H_{14}O_4Na$ $[M + Na]^+$: 209.0790; found: 209.0787.

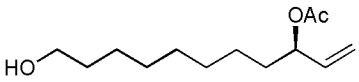


Entry 5. Run 1: 230 mg, 0.806 mmol, 81% yield, [B:L] = 4.5:1, [ee] = 55%. Run 2: 248 mg, 0.861 mmol, 86% yield; [B:L] = 4.1:1, [ee] = 52%. Run 3: 229 mg, 0.802 mmol, 80% yield; [B:L] = 4.6:1, [ee] = 55%. (β-cyclodextrin, 140°C isothermal, t_R(major) = 93.29 min., t_R(minor) = 95.48 min. [**average yield:** 82%, with 6% recovered SM (13.6 mg)]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.76 (ddd, J = 17.2, 10.4, 6.2 Hz, 1H), 5.24-5.14 (m, 3H), 3.68 (s, 3H), 3.17 (s, 3H), 2.40 (t, J = 7.6 Hz, 2H), 2.06 (s, 3H), 1.63-1.54 (m, 4H), 1.30 (bs, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.7, 170.4, 136.5, 116.5, 74.8, 61.1, 34.1, 32.2, 31.8, 29.3, 29.2, 29.2, 24.9, 24.5, 21.2; **IR** (neat, cm^{-1}) 3084.1, 2936.7, 2854.6, 1737.9, 1665.9, 1463.3, 1383.0, 1239.8; **HRMS** (ESI) m/z calculated for $C_{15}H_{27}NO_4Na$ $[M + Na]^+$: 308.1838; found: 308.1832.

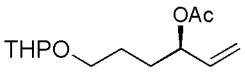


Entry 6. Run 1: 381 mg, 0.816 mmol, 82% yield, [B:L] = 4.4:1, [ee] = 63%. Run 2: 386 mg, 0.826 mmol, 83% yield; [B:L] = 4.6:1, [ee] = 64%. Run 3: 402 mg, 0.862 mmol, 86% yield; [B:L] = 4.3:1, [ee] = 61%. EE determination performed after silyl deprotection (1M TBAF in THF) and acetylation (Ac_2O, NEt_3, DMAP). (β-cyclodextrin, 135°C isothermal, t_R(major) = 36.86 min., t_R(minor) = 37.92 min.) [**average yield:** 84%, with 7% recovered SM (28.5 mg)]; **^{1}H NMR**

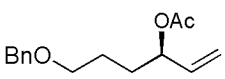
(500 MHz, $CDCl_3$) δ 7.67 (dd, J = 7.8, 1.0 Hz, 4H), 7.47-7.34 (m, 6H), 5.77 (ddd, J = 17.4, 10.5, 6.5 Hz, 1H), 5.25-5.14 (m, 3H), 3.65 (t, J = 6.5 Hz, 2H), 2.06 (s, 3H), 1.65-1.52 (m, 4H), 1.40-1.20 (m, 10H), 1.04 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.4, 136.6, 135.6, 134.1, 129.5, 127.5, 116.5, 74.9, 64.0, 34.2, 32.5, 29.4, 29.3, 29.3, 26.9, 25.7, 25.0, 21.3, 19.2; **IR** (neat, cm^{-1}) 3071.3, 3050.2, 2931.0, 2857.8, 1741.0, 1589.5, 1472.3, 1428.0, 1240.5; **HRMS** (ESI) m/z calculated for $C_{29}H_{42}O_3SiNa$ $[M + Na]^+$: 489.2801; found: 489.2803.



Entry 7. Run 1: 189 mg, 0.829 mmol, 83% yield, [B:L] = 4.9:1, [ee] = 50%. Run 2: 187 mg, 0.819 mmol, 82% yield; [B:L] = 3.7:1, [ee] = 49%. Run 3: 189 mg, 0.827 mmol, 83% yield; [B:L] = 4.6:1, [ee] = 50%. EE determination performed after acetylation (Ac_2O, NEt_3, DMAP). (β-cyclodextrin, 135°C isothermal, t_R(major) = 36.92 min., t_R(minor) = 37.94 min.), [**average yield:** 83%.]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.77 (ddd, J = 17.4, 10.5, 6.5 Hz, 1H), 5.25 (m, 3H), 3.64 (app dd, J = 12.0, 6.5 Hz, 2H), 2.06 (s, 3H), 1.67-1.53 (m, 4H), 1.40-1.23 (m, 10H),; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.4, 136.6, 116.5, 74.8, 63.0, 34.1, 32.7, 29.4, 29.3, 29.2, 25.6, 25.0, 21.2; **IR** (neat, cm^{-1}) 3247.5, 3085.2, 2931.4, 2856.6, 1731.8, 1647.3, 1463.4, 1371.9; **HRMS** (ESI) m/z calculated for $C_{13}H_{24}O_3Na$ $[M + Na]^+$: 251.1623; found: 251.1620.

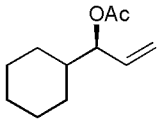


Entry 8. Run 1: 220 mg, 0.908 mmol, 91% yield, [B:L] = 3.6:1, [ee] = 50%. Run 2: 220 mg, 0.908 mmol, 91% yield; [B:L] = 3.3:1, [ee] = 47%. Run 3: 221 mg, 0.914 mmol, 91% yield; [B:L] = 3.8:1, [ee] = 49%. EE determination done after converting THP to acetate.[80] (β-cyclodextrin, 110°C isothermal, t_R(major) = 9.27 min., t_R(minor) = 9.80 min.), [**average yield:** 91%.]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.78 (ddd, J = 17.0, 10.5, 6.5 Hz, 1H), 5.30-5.16 (m, 3H), 4.57 (t, J = 3.5 Hz, 1H), 3.88-3.83 (m, 1H), 3.77-3.71 (m, 1H), 3.52-3.47 (m, 1H),3.42-3.36 (m, 1H), 2.06 (s, 3H), 1.88-1.49 (m, J = 10H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.3, 136.3, 116.7, 98.8, 74.6, 67.0, 62.3, 30.9, 30.7, 25.4, 25.3, 21.2, 19.6; **IR** (neat, cm^{-1}) 3087.1, 2937.0, 2870.7, 1738.4, 1646.7,1441.31, 1371.7, 1236.9; **HRMS** (ESI) m/z calculated for $C_{13}H_{22}O_4Na$ $[M + Na]^+$: 265.1416; found: 265.1410.



Entry 9. Run 1: 225 mg, 0.906 mmol, 91% yield, [B:L] = 4.7:1, [ee] = 45%. Run 2: 226

mg, 0.910 mmol, 91% yield; [B:L] = 4.7:1, [ee] = 44%. Run 3: mg, mmol, 89% yield; [B:L] = 3.6:1, [ee] = 45%. (β-cyclodextrin, 140°C isothermal, t_R(major) = 21.87 min., t_R(minor) = 22.39 min.), [**average yield:** 91%.]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 5.77 (ddd, J = 17.2, 10.4, 6.2 Hz, 1H), 5.28-5.15 (m, 3H), 4.50 (bs, 2H), 3.48 (t, J = 6.4 Hz, 2H), 2.06 (s, 3H), 1.75-1.60 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.3, 138.4, 136.3, 128.3, 127.6, 127.5, 116.7, 74.5, 72.9, 69.8, 30.8, 25.4, 21.2; **IR** (neat, cm^{-1}) 3087.8, 3063.9, 3031.2, 2940.3, 2857.9, 1737.7, 1647.0, 1496.0, 1454.1; **HRMS** (ESI) m/z calculated for $C_{15}H_{20}O_3Na$ $[M + Na]^+$: 271.1310; found: 271.1302.



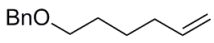
Entry 10. Run 1: 144 mg, 0.791 mmol, 79% yield, [B:L] =1.5:1, [ee] = 62%. Run 2: 141 mg, 0.772 mmol, 77% yield; [B:L] = 1.5:1, [ee] = 61%, (β-cyclodextrin, 110°C isothermal, t_R(major) = 5.24 min., t_R(minor) = 5.52 min.), [**average yield:** 78%, with 6% recovered SM (7.5 mg)]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.75 (ddd, J = 17.1, 10.5, 7.0 Hz, 1H), 5.23-5.17 (m, 2H), 5.04 (t, J = 7.0 Hz, 1H), 2.07 (s, 3H), 1.75-1.49 (m, 6H), 1.33-0.88 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.4, 135.1, 117.4, 78.9, 41.4, 28.5, 26.3, 26.1, 25.9, 25.9, 21.2; **IR** (neat, cm^{-1}) 3087.0, 2926.7, 2853.7, 1741.6, 1450.1, 1369.6; **HRMS** (ESI) m/z calculated for $C_{11}H_{18}O_2Na$ $[M + Na]^+$: m/z calculated for $C_{11}H_{18}O_2Na$ $[M + Na]^+$: 205.1204; found: 205.1196

General Procedure for Cleavage of Allylic Acetates: To a 25 mL flask containing crude allylic acetate (1 mmol, assumed) was added MeOH (5 mL, 0.2 M) and potassium carbonate (0.276 g, 2 mmol). The reaction was vigorously stirred and monitored via thin layer chromatography (TLC). Upon completion, the reaction was transferred to a sepratory funnel with methylene chloride (50 mL). Water (15 mL) was added, and the aqueous layer was extracted with methylene chloride (3 x 50 mL). The combined organics were washed with brine (1 x 10 mL), then dried ($MgSO_4$), filtered, and reduced *in vacuo*. Products were then purified by standard SiO_2 chromatography. While the branched and linear allylic alcohols were commonly separable, it was found that carrying them forward as a mixture had no detrimental effect as the subsequent resolution acylated the linear alcohol rapidly making its separation from branched alcohol trivial. Individual product yields and characterization are reported below.

General Procedure for Resolution with Novozyme 435: To a flame dried round bottom flask containing allylic alcohol to be resolved (1 equiv.) was added vinyl acetate (0.6M) and Novozyme 435 immobilized on polystyrene

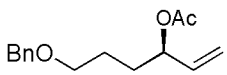
beads (33.3 mg/1 mmol). The reaction was stirred vigorously at room temperature for 36 hrs. Upon completion, the solid supported enzyme was removed via filtration. The solid support was rinsed thoroughly with diethyl ether and then the filtrate reduced *in vacuo* and purified via standard SiO_2 chromatography. Enantioselectivities were determined by chiral gas chromatographic analysis on the acetylated derivative of each isolated alcohol. It was found that the recovered solid supported enzyme could be used up to 5 times with little diminishment in activity. Individual yields and selectivities are reported below.

General Procedure for Resolution with the Protease *S. Carlsberg*: The active enzyme for resolution was prepared as previously described by and co-workers.[81] To a flame dried round bottom flask containing allylic alcohol to be resolved (1 equiv.) was added isoproenyl valerate[82] (1.5 equiv), active S. Carlsberg (36 mg/1 mmol), sodium carbonate (1 equiv.) and THF (0.5M). The reaction was stirred vigorously at room temperature for 60 hrs. Upon completion, the enzyme was removed via filtration. The enzyme was rinsed thoroughly with diethyl ether and then the filtrate reduced *in vacuo* and purified via standard SiO_2 chromatography. Enantioselectivities were determined by chiral gas chromatographic analysis on the acetylated derivative of each isolated alcohol. Individual yields and selectivities are reported below.



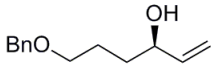
1-O-Benzyl-5-hexen-1-ol (29) To a flame dried 100 mL round bottom flask was added NaH (0.624 g, 26.0 mmol, 2 equiv.) under inert atmosphere. The flask was then charged with a Teflon stir bar, sealed with a septum, and anhydrous DMF (65 mL, 0.2M) was added. After cooling the reaction vessel to 0°C, 5-hexen-1-ol (1.3 g, 13.0 mmol, 1 equiv.) was added dropwise via syringe and allowed to stir at 0°C for 1 hour. Benzyl bromide (1.62 mL, 13.6 mmol, 1.05 equiv.) was then added dropwise via syringe, and the reaction was allowed to warm to room temperature. After the reaction had gone to completion by TLC analysis, the reaction flask was again cooled in an ice bath and quenched with saturated, aqueous NH_4Cl solution (50 ml). The reaction was then transferred to a sepratory funnel and diluted with 200 mL of Et_2O. The organic layer was collected, and the aqueous layer was extracted further with Et_2O (3 x 50 mL). The combined organics were then dried ($MgSO_4$), filtered, and reduced *in vacuo*. The crude material was then purified via column chromatography using a 10:90 EtOAc:Hexanes eluent system to afford **29** as a clear oil (2.43 g, 12.7 mmol, **98% yield**) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37-7.32 (m, 4H), 7.30-7.26 (m, 1H), 5.81 (ddt, J = 7.0, 10.0,

17.0 Hz, 1H), 5.00 (dm, J = 17.3 Hz, 1H), 4.95 (dm, J = 10.5 Hz, 1H), 4.51 (s, 2H), 3.48 (t, J = 6.5 Hz, 2H), 2.07 (app q, J = 7.0 Hz, 2H), 1.64 (app p, J = 6.5 Hz, 2H), 1.48 (app p, J = 7.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.7, 138.6, 128.3, 127.5, 127.4, 114.5, 72.8, 70.2, 33.5, 29.2, 25.4; **IR** (neat, cm^{-1}) 3064.4, 3029.6, 2975.6, 2935.1, 2858.0, 2794.4, 1641.1, 1496.5, 1454.1; **HRMS** (EI) m/z calculated for $C_{13}H_{18}O$ $[M+]^+$: 190.13577; found 190.13445.



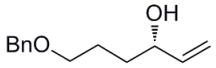
(*4R*)-1-O-Benzyl-4-acetoxy-5-hexen-1,4-diol: Following the general procedure for the asymmetric branched allylic oxidation afforded: Run 1: 226 mg, 0.910 mmol, 91% yield; [B:L] = 4.7:1, [ee] = 44%. Run 2: 220 mg, 0.886 mmol, 89% yield; [B:L] = 3.8:1, [ee] = 45%. (β-cyclodextrin, 120°C isothermal, t_R(R) = 64.98 min., t_R(S) = 66.64 min.), [**average yield:** 90%.]; This material was taken forward without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 5.77 (ddd, J = 17.2, 10.4, 6.2 Hz, 1H), 5.28-5.15 (m, 3H), 4.50 (bs, 2H), 3.48 (t, J = 6.4 Hz, 2H), 2.06 (s, 3H), 1.75-1.60 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.3, 138.4, 136.3, 128.3, 127.6, 127.5, 116.7, 74.5, 72.9, 69.8, 30.8, 25.4, 21.2; **IR** (neat, cm^{-1}) 3087.8, 3063.9, 3031.2, 2940.3, 2857.9, 1737.7, 1647.0, 1496.0, 1454.1; **HRMS** (ESI) m/z calculated for $C_{15}H_{20}O_3Na$ $[M + Na]^+$: 271.1310; found: 271.1302.

This material was then subjected to the standard procedure for cleavage of the allylic acetate which afforded allylic alcohol ready for subsequent resolution: Run 1: 185 mg, 0.897 mmol, 99% yield, [B:L] = 4.7:1. Run 2: 181 mg, 0.877 mmol, 99% yield; [B:L] = 3.8:1

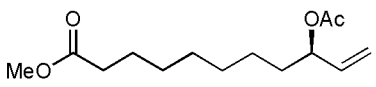


(-)-(*4R*)-1-O-Benzyl-5-hexen-1,4-diol ((-)-**24**)**:** Following the general procedure for Novozyme 435 resolution afforded: Run 1: 105 mg, 0.509 mmol, 57% yield, [B:L] = >20:1, [ee] = 98%. Run 2: 100 mg, 0.485 mmol, 55% yield; [B:L] = >20:1, [ee] = 99%. Enantiomeric access was determined on the acylated derivative of the final product (ee determined on the acylated alcohol, β-cyclodextrin, 120°C isothermal, t_R(R) = 65.56 min., t_R(S) = 67.14 min), [**average yield:** 56%.]; **$[\alpha]^{26}_D$** = -2.86° (c = 2.0, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37-7.32 (m, 4H), 7.30-7.25 (m, 1H), 5.87 (ddd, J = 17.0, 10.5, 6.0 Hz, 1H), 5.25 (dt, J = 17.0, 1.5 Hz, 1H), 5.10 (dt, J = 10.5, 1.5 Hz, 1H), 4.52 (s, 2H), 4.13 (m, 1H), 3.52 (t, J = 6.0 Hz, 2H), 2.27 (d, J = 4.5 Hz, 2H), 1.77-1.57 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 141.0, 138.1, 128.3, 127.6, 127.6, 114.4, 72.9, 72.6, 70.2, 34.2, 25.7; **IR** (neat, cm^{-1}) 3403.8, 3066.3, 3031.6, 2979.5, 2942.9, 2858.0,

2798.2, 1643.1.0, 1496.5, 1454.1; **HRMS** (ESI) m/z calculated for $C_{13}H_{18}O_2Na$ $[M+Na]^+$: 229.1204; found: 229.1204.

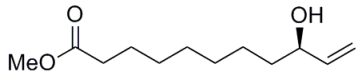


(+)-(*4S*)-1-O-Benzyl-5-hexen-1,4-diol ((+**)-24):** Material for this route was obtained by application of the general ABAO procedure using (S,S)-**19** as a chiral catalyst. Subsequent acetate deprotection by the general procedure described afforded: Run 1: 180 mg, 0.873 mmol, 87% yield; [B:L] = 4.4:1, [ee] = 46%. Run 2: 187 mg, 0.906 mmol, 91% yield; [B:L] = 4.1:1, [ee] = 45%. Yields and selectivities are over two-steps. This material was then subjected to the general procedure for resolution with *S. Carlsberg* to afford chiral allylic alcohol: Run 1: 92 mg, 0.446 mmol, 52% yield, [B:L] = >20:1, [ee] = 99%. Run 2: 97 mg, 0.470 mmol, 54% yield; [B:L] = >20:1, [ee]; Enantiomeric access was determined on the acylated derivative of the final product (ee determined on the acylated alcohol, β-cyclodextrin, 120°C isothermal, t_R(S) = 67.03 min) [**average yield:** 53%.]; $[\alpha]^{26}_D$ = +2.85° (c = 2.0, $CHCl_3$).

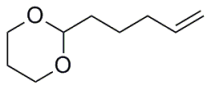


Methyl (*9R*)-9-acetoxyundec-10-eneoate: The general procedure for the asymmetric branched allylic oxidation afforded: Run 1: 235 mg, 0.915 mmol, 92% yield, [B:L] = 5.1:1, [ee] = 58%. Run 2: 224 mg, 0.876 mmol, 88% yield; [B:L] = 4.3:1, [ee] = 55%. Run 3 (gram scale): 1.09 g, 4.250 mmol, 85% yield; [B:L] = 4.1:1, [ee] = 57%. (β-cyclodextrin, 120°C isothermal, t_R(R) = 55.96 min., t_R(S) = 57.30 min.), [**average yield:** 90%]; This material was taken forward without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.78 (ddd, J = 17.1, 10.5, 6.5 Hz, 1H), 5.24-5.14 (m, 3H), 3.66 (s, 3H), 2.29 (t, J = 8.0 Hz, 2H), 2.05 (s, 3H), 1.62-1.53 (m, 4H), 1.29 (bs, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.2, 170.3, 136.5, 116.5, 74.8, 51.4, 34.1, 34.0, 29.1, 29.0, 29.0, 24.9, 24.8, 21.2; **IR** (neat, cm^{-1}) 3089.1, 2932.9, 2858.2, 1742.0, 1436.3, 1371.5; **HRMS** (ESI) m/z calculated for $C_{14}H_{24}O_4Na$ $[M + Na]^+$: 279.1572; found: 279.1564.

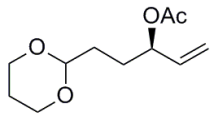
This material was then subjected to the standard procedure for cleavage of the allylic acetate which afforded allylic alcohol ready for subsequent resolution: Run 1: 188 mg, 0.877 mmol, 96% yield, [B:L] = 5.1:1. Run 2: 179 mg, 0.835 mmol, 95% yield; [B:L] = 4.3:1. Run 3 (gram scale): 879 mg, 4.101 mmol, 96% yield; [B:L] = 4.1:1



Methyl (*9R*)-9-hydroxyundec-10-eneoate ((-)-30): Following the general procedure for Novozyme 435 resolution afforded: Run 1: 119 mg, 0.555 mmol, 63% yield, [B:L] = >20:1, [ee] = 99%. Run 2: 109 mg, 0.509 mmol, 61% yield; [B:L] = >20:1, [ee] = 98%, Run 3 (gram scale): 523 mg, 2.441 mmol, 60% yield; [B:L] = >20:1, [ee] = 99%. (ee determined on the acylated alcohol, β-cyclodextrin, 120°C isothermal, t_R(R) = 55.92 min.), [**average yield:** 62%]; **[α]$^{25}_{D}$** = -5.13° (c = 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.86 (ddd, J = 16.9, 10.8, 6.0 Hz, 1H), 5.22 (d, J = 17.0 Hz, 1H), 5.10 (d, J = 10.5 Hz, 1H), 4.09 (p, J = 5.5 Hz, 1H), 3.66 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 1.63 – 1.30 (m, 13H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.2, 141.3, 114.4, 73.2, 51.4, 37.0, 34.1, 29.3, 29.1, 29.0, 25.2, 24.9; **IR** (neat, cm^{-1}) 3426.9, 2979.5, 2931.3, 2856.1, 1739.5, 1436.7; **HRMS** (ESI) m/z calculated for $C_{12}H_{22}O_3Na$ $[M+Na]^+$: 237.1467; found: 237.1471.

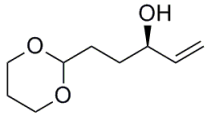


2-(Pent-4-en-1-yl)-1,3-dioxane (**36**)**:** To a flame dried 100 mL round bottom flask with a Teflon stir bar under an inert atmosphere of N_2 was added THF (34 mL, 0.15M) and bromoethyl-1,3-dioxane (1.0 g, 5.123 mmol, 1 equiv.). A 2M solution of allylmagnesium chloride in THF (10.25 mL, 20.04 mmol, 4 equiv.) was then added dropwise via syringe. The reaction was heated to reflux briefly (~10 min.) and then allowed to cool to room temperature and stir overnight. The reaction was complete by TLC analysis, and the reaction slowly quenched with saturated, aqueous NH_4Cl solution (50 ml). The reaction was then transferred to a separatory funnel and diluted with 150 mL of Et_2O. The organic layer was collected, and the aqueous layer was extracted further with Et_2O (3 x 50 mL). The combined organics were then washed with H_2O (2 x 15 mL), dried ($MgSO_4$), filtered, and reduced *in vacuo*. The crude material was then purified via column chromatography using a 10:90 EtOAc:Hexanes eluent system to afford a clear oil (0.793 g, 5.08 mmol, **99% yield**) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.80 (ddt, J = 6.5, 10.0, 17.3 Hz, 1H), 5.00 (dm, J = 17.3 Hz, 1H), 4.94 (dm, J = 10.0 Hz, 1H), 4.52 (t, J = 5.5 Hz, 1H), 4.12-4.07 (m, 2H), 3.79-3.72 (m, 2H), 2.12-2.02 (m, 3H), 1.63-1.57 (m, 2H) 1.52-1.45 (m, 2H) 1.33 (d heptet, J = 1.5, 13.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.5, 114.7, 102.2, 66.9, 34.3, 33.5, 25.8, 23.2; **IR** (neat, cm^{-1}) 3075.9, 2954.4, 2925.5, 2850.3, 2778.9, 2730.7, 2657.4, 1641.1, 1459.9; **HRMS** (EI) m/z calculated for $C_9H_{15}O_2$ $[M-H]^+$: 155.10721; found: 155.10588.

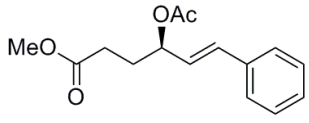


2-((*3R*)-Pent-3-acetoxy-4-en-1-yl-3-ol)-1,3-dioxane: Following the general procedure for the asymmetric branched allylic oxidation afforded: Run 1: 180 mg, 0.840 mmol, 84% yield; [B:L] = 4.8:1:1, [ee] = 44%. Run 2: 178 mg, 0.831 mmol, 83% yield; [B:L] = 4.3:1, [ee] = 46%. (β-cyclodextrin, 110°C isothermal, t_R(R) = 22.21 min., t_R(S) = 22.79 min.), [**average yield:** 84%.]; This material was taken forward without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.76 (ddd, J = 6.5, 10.5, 17.3 Hz, 1H), 5.24 (q, J = 6.5 Hz, 1H), 5.23 (dm, J = 17.5 Hz, 1H), 5.16 (dm, J = 10.5 Hz, 1H), 4.53 (t, J = 5.0 Hz, 1H), 4.09 (m, 2H), 3.75 (dt, J = 3.0, 12.5 Hz, 2H), 2.12-2.02 (m, 1H), 2.06 (s, 3H), 1.78-1.58 (m, 4H), 1.33 (dm, J = 13.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.2, 136.3, 116.7, 101.7, 74.3, 66.9, 30.7, 28.5, 25.8, 21.1; **IR** (neat, cm^{-1}) 3087.5, 2962.1, 2931.3, 2852.2, 2780.9, 2732.7, 2661.3, 1739.5, 1646.9, 1430.9, 1407.8; **HRMS** (ESI) m/z calculated for $C_{11}H_{18}O_4Na$ $[M+Na]^+$: 237.1103; found 237.1104.

This material was then subjected to the standard procedure for cleavage of the allylic acetate which afforded allylic alcohol ready for subsequent resolution: Run 1: 141 mg, 0.819 mmol, 97% yield, [B:L] = 4.8:1. Run 2: 135 mg, 0.784 mmol, 94% yield; [B:L] = 4.3:1

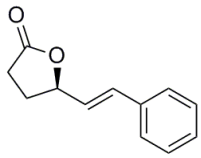


2-((*3R*)-Pent-4-en-1-yl-3-ol)-1,3-dioxane ((-)-34): Following the general procedure for Novozyme 435 resolution afforded: Run 1: 80 mg, 0.464 mmol, 57% yield; [B:L] = >20:1:1, [ee] = 99%. Run 2: 76 mg, 0.441 mmol, 56% yield; [B:L] = >20:1, [ee] = 99%. (ee determined on the acylated alcohol, β-cyclodextrin, 110°C isothermal, t_R(R) = 22.31 min., t_R(minor) = 22.93 min.), [**average yield:** 57%.]; **$[\alpha]^{24}_D$** = -5.01° (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.86 (ddd, J = 5.6, 10.4, 17.3 Hz, 1H), 5.24 (dt, J = 1.6, 17.2 Hz, 1H), 5.10 (dt, J = 1.2, 10.8 Hz, 1H), 4.58 (t, J = 4.4 Hz, 1H), 4.18-4.08 (m, 3H), 3.77 (app t, J = 11.6 Hz, 2H), 2.36 (d, J = 4.0 Hz, 1H), 2.08 (qt, J = 4.0, 12.4, 1H), 1.78-1.58 (m, 4H), 1.35 (d sep, J = 1.2, 13.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 141.0, 114.4, 102.1, 72.6, 66.9, 31.2, 31.1, 25.7; **IR** (neat, cm^{-1}) 3430.8, 3079.8, 2962.1, 2929.4, 2856.1, 2734.6, 1643.1, 1429.0, 1405.9; **HRMS** (ESI) m/z calculated for $C_9H_{16}O_3Na$ $[M+Na]^+$: 195.0995; found 195.0997.



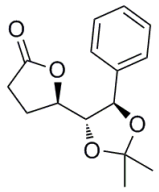
(*4R, E*)-Methyl 4-acetoxy-6-phenylhex-5-enoate (40): A round bottom flask (25 mL) was charged with the following: 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate(**13**) (10 mol%, 0.50 mmol, 250 mg); (1R,2R)-(-)-[1,2-Cyclohexanediamino-N,N'-bis(3,5-di-t-

butylsalicylidene)] Chromium(III)F(*R,R*-**19)** (10 mol%, 0.50 mmol, 308 mg), 1,4-benzoquinone (2 equiv., 10.0 mmol, 1.08 g), an activated 4Å MS bead (~30 mg), and a Teflon© stir bar. A separate vial (2 mL, borosilicate) was charged with the following: Methyl hexenoate (1.0 equiv, 5.0 mmol, 0.704 mL), AcOH (1.1 equiv., 5.5 mmol, 0.315 mL), and EtOAc (0.50 mL). The liquids were transferred to the solids via pipette and the vial rinsed with EtOAc (4 x 0.50 mL). After carefully stirring for 48 hrs at room temperature, to the reaction was added phenyl boronic acid (1.5 equiv., 7.5 mmol, 0.914 g), AcOH (1 equiv., 5 mmol, 0.285 mL), and EtOAc (12.5 mL). The reaction was stirred at room temperature until complete by TLC (~4 hr) at which point the reaction mixture was transferred to a separatory funnel with ~5 mL EtOAc and diluted with hexanes (400 mL). The organic layer was rinsed with sat. aq. $NaHSO_3$ (1 x 50 mL) and 5% aq. K_2CO_3 (2 x 50 mL). *Caution should be taken when combining aqueous layers as carbon dioxide is evolved.* The combined aqueous layers were back extracted with hexanes (100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and reduced *in vacuo.* The resulting oil was re-dissolved in hexanes (150 mL) and extracted again with 5% aq. K_2CO_3 (3 x 25 mL) to remove residual hydroquinone. The organic layer was again dried ($MgSO_4$), filtered and reduced *in vacuo* This product was generally taken forward without further purification, but was isolated and purified via silica gel chromatography for characterization. [B:L] = >20:1, [ee] = 50%. (Determined on the initial branched acetate product prior to oxidative Heck reaction, β-cyclodextrin, 110°C isothermal, t_R(R) = 5.52 min., t_R(S) = 5.83 min.), **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.31-7.25 (m, 1H), 6.64 (d, J = 16.0 Hz, 1H), 6.12 (dd, J = 7.5, 15.8 Hz, 1H), 5.46 (q, J = 6.5 Hz, 1H), 3.68 (s, 3H), 2.42 (dt, J = 2.0, 7.8 Hz, 2H), 2.13-2.07 (m, 2H), 2.10 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.2, 170.2, 136.0, 133.0, 128.5, 128.0 126.7, 126.6, 73.7, 51.7, 29.8, 29.5, 21.2; **IR** (neat, cm^{-1}) 3085.6, 3025.8, 2952.5, 2848.4,v1737.6, 1658.5, 1598.7, 1597.4, 1494.6; **HRMS** (ESI) m/z calculated for $C_{15}H_{18}O_4Na$ $[M+Na]^+$: 285.1103; found 285.1092.



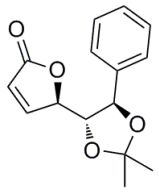
(*R, E*)-5-styryldihydrofuran-2(3H)-one (41): To crude **40** (5 mmol, assumed) in a round bottom flask (250 mL) was added THF (18.75 mL), DI H_2O (6.25 mL), and a Teflon© stir bar. The flask was cooled to 0°C and $LiOH{\cdot}H_2O$ (0.623 g, 15 mmol, 3.0 equiv.) was added in one portion. The ice bath was removed after 10 minutes and the reaction monitored via TLC. Upon completion (~2-4 hr) benzene (150 mL) was added and the flask was transferred to a 100°C oil bath and a Dean-Stark trap and a reflux condenser were added. The reaction was brought to a comfortable reflux and then allowed to stir overnight. After

removing the flask from the bath and allowing it to cool to room temperature, the contents were transferred to a separatory funnel and the organic layer washed with aq. 1M H_3PO_4 (3 x 25 mL). The organic layer was then dried ($MgSO_4$), filtered, and reduced *in vacuo.* The resulting off white solid was purified via silica gel chromatography (10-30% Et_2O:Hexanes) to afford a white solid. (0.504 g, 2.678 mmol, 54% (2-step)) **^{1}H NMR** (500 MHz, $CDCl_3$) δ7.40 (d, J = 7.5 Hz, 2H), 7.37-7.32 (m, 2H), 7.30-7.26 (m, 1H), 6.69 (d, J = 16.0 Hz, 1H), 6.21 (dd, J = 6.5, 16.0 Hz, 1H), 5.13 (q, J = 6.5 Hz, 1H), 2.65-2.54 (m, 2H), 2.50 (app sextuplet, J = 9.0 Hz, 1H), 2.11 (ddd, J = 9.0, 12.5, 16.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.9, 135.6, 132.9, 128.7, 128.4 126.7, 126.4, 80.5, 28.8, 28.5; **IR** (neat, cm^{-1}) 2989.1, 2950.6, 1762.6, 1722.1, 1454.1, 1415.5; **HRMS** (ESI) m/z calculated for $C_{12}H_{13}O_2$ $[M+H]^+$: 189.0916; found 189.0918.



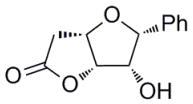
(R)-5-((4R,5R)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl)dihydrofuran-2(3H)-one ((-)-42): To a clean, dry 100 mL recovery flask was added sequentially the following: $K_2OsO_4 \cdot 2H_2O$ (0.018 g, 0.05 mmol, 1 mol%), $(DHQD)_2PHAL$ (0.199 g, 0.25 mmol, 5 mol%), $K_3Fe(CN)_6$ (4.94 g, 15 mmol, 3 equiv.), K_2CO_3 (2.07 g, 15 mmol, 3 equiv.), $NaHCO_3$ (1.34 g, 15 mmol, 3 equiv.), a Teflon© stir bar, deionized water (24 mL), and *tert*-butanol (24 mL). The reaction flask was stirred vigorously until both layers became translucent, at which time $MeSO_2NH_2$ (0.476 g, 5 mmol, 1 equiv.) was added and the reaction was cooled to 0°C. After the solution became opaque, olefin **(41)** (0.941 g, 5 mmol, 1 equiv.) was added in one portion. CH_2Cl_2 (2.4 mL) was added to improve SM solubility and the reaction was stirred vigorously at 0°C for 1 hr, then warmed to room temperature and stirred until completion as indicated by TLC (~5 hr). Upon completion, sodium bisulfite (2 g) was added slowly and the reaction stirred for 1 hour. The reaction mixture was transferred to a separatory funnel and EtOAc (50 ml) was added. The aqueous layer was extracted with additional EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. To the crude diol was added DMF (8.4 mL, 0.6 M) and 2-methoxypropene (4.79 mL). The reaction was cooled to 0°C and *p*-$TsOH \cdot H_2O$ (0.238 g, 1.25 mmol, 0.25 equiv.) was added and the reaction allowed to warm to room temperature while stirring overnight. The reaction mixture was then transferred to a separatory funnel and diluted with Et_2O (200 mL). The organic layer was washed with DI H_2O (3 x 25mL) and brine (1 x 25 mL). The organic layer was then dried ($MgSO_4$), filtered, and reduced *in vacuo*. Residual DMF or 2-methoxypropene was removed by addition of benzene and *in vacuo* concentration. The crude oil was purified by silica gel chromatography in 10-40% Et_2O:Hexanes to

afford a white solid (0.920 g, 3.52 mmol, 70% yield (2-step), >20:1 dr, 99% ee (Determined on Chiracel AD-RH , 35:75 $CH_3CN:H_2O$, t_R(major) = 7.3 min., t_R(minor) = 6.8 min.) $[\alpha]^{26}_D$ = -94.9° (c = 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ7.39-7.31 (m, 5H), 4.78 (d, J = 8.5 Hz, 1H), 4.60 (ddd, J = 4.0, 6.3, 7.5 Hz, 1H), 4.10 (dd, J = 4.0, 8.3 Hz, 1H), 2.60 (ddd, J = 6.5, 10.0, 18.0 Hz, 1H), 2.51 (ddd, J = 7.5, 9.5, 17.4 Hz, 1H), 2.38-2.24 (m, 2H), 1.56 (s, 3H), 1.52 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.5, 137.2, 128.8, 128.7, 126.7 110.2, 83.4, 80.1, 78.7, 28.1, 27.1, 27.0, 22.9; **IR** (neat, cm^{-1}) 3066.3, 3031.6, 2985.3, 2935.1, 2980.8, 1781.9, 1604.5, 1494.6, 1456.0; **HRMS** (ESI) m/z calculated for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1283; found 263.1280. The absolute configuration of this molecule was determined on a crystal grown from benzene of *p*-bromophenyl-**42** synthesized through the same sequence. The structure and pertinent measurements can be found in Appendix B.



(R)-5-((4R,5R)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl)furan-2(5H)-one ((+)-43): To a clean, flame dried 25 mL recovery flask charged with a Teflon stir bar and under an argon atmosphere was added THF (5 mL) and hexamethyldisilazane (1.36 mmol, 0.288 mL, 1.1 equiv.). The reaction was cooled to -78°C, and n-Buli (1.30 mmol, 0.813 mL, 1.05 equiv.) was added dropwise via syringe. After stirring for ten minutes, **(-)-42** (1.24 mmol, 0.325 g, 1 equiv.) in THF (1 mL, 0.15 mL rinse) was added slowly via cannula. The reaction was stirred a further 25 minutes, and then phenylselenyl bromide (1.24 mmol, 0.293 g, 1 equiv.) in THF (1.15 mL) was added via cannula over ~10 min. The reaction was stirred for an additional 5 minutes and then quenched at-78°C with 1N HCl (5 mL). The reaction mixture was transferred to a separatory funnel and diluted with Et_2O (200 ml). The organic layer was washed with sat. aq. $NaHCO_3$ (2 x 10 mL). The organic layer was then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. *Reproducibility for the elimination step was significantly improved by quickly purifying away fast running selenium containing species by SiO_2 chromatography in 5%-10%-20% Et_2O:Hexanes*. To the mixture of selenides (1.03 mmol, 0.425 g, 1 equiv.) in a clean, dry 100 mL flask was added CH_2Cl_2 (20.6 mL, 0.05 M) and the reaction flask was cooled to 0°C in an ice bath. Hydrogen peroxide (3.08 mmol, 0.346 mL of 30% solution, 3 equiv.) was then added slowly via syringe. The reaction was stirred at 0C and conversion monitored by TLC. Upon completion, the reaction mixture was transferred to a separatory funnel and CH_2Cl_2 was added (200 mL). The organic layer was then washed with DI H_2O (2 x 20 mL) and brine (20 mL). The organic layer was then dried ($MgSO_4$), filtered, and reduced *in vacuo*. The crude oil was purified by silica gel chromatography in 10-40% Et_2O:Hexanes to afford a white solid (0.237 g,

0.91 mmol, 73% yield (2-step). **[α]$^{25}_{D}$** = 555.6° (c = 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ7.48 (dd, J = 1.5, 6.0 Hz, 1H), 7.40-7.31 (m, 5H), 6.17 (dd, J = 2.5, 5.8Hz, 1H), 5.16 (dt, J = 2.0, 6.5 Hz, 1H), 5.02 (d, J = 8.0 Hz, 1H), 3.91 (dd, J = 6.5, 7.5 Hz, 1H), 1.56 (s, 3H), 1.54 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.2, 153.8, 137.3, 128.6, 128.6, 127.0, 122.6, 110.6, 82.8, 82.7, 80.7, 27.1, 26.8; **IR** (neat, cm^{-1}) 3089.4, 3033.5, 2989.1, 2935.1, 2894.6, 1783.8, 1758.8, 1602.6, 1496.5, 1456.0; **HRMS** (ESI) m/z calculated for $C_{15}H_{17}O_4$ $[M+H]^+$: 261.1127; found 263.1123.



(3aS,5R,6S,6aS)-6-hydroxy-5-phenyltetrahydrofuro[3,2-b]furan-2(5H)-one ((-)-44): To **(+)-43** (0.91 mmol, 0.237 g, 1 equiv.) in a clean, dry round bottom flask (50 mL) with a Teflon© stir bar was added THF (9.1 mL) and 1N HCl (5-10 drops). The reaction mixture was heated to 45C and monitored via TLC (70% EtOAc:Hex). Deprotection and cyclization would generally proceed to completion under these conditions with prolonged stirring, but could be expedited by the following procedure. After complete acetonide deprotection by TLC, the flask was cooled to 0°C and CH_2Cl_2 (9.1 mL) and NEt_3 was added until a pH of ~10 was obtained. The flask was then allowed to warm to room temperature and monitored via TLC. Upon completion (~4-6 hr), the contents were transferred to a separatory funnel and diluted with further CH_2Cl_2. The organic layer was then washed with sat. aq. NH_4Cl solution (3 x 15 mL). The combined aqueous layers were back extracted with EtOAc (3 x 50 mL) and then the combined organic layers were dried ($MgSO_4$), filtered, and reduced *in vacuo*. The resulting off white solid was purified via silica gel chromatography (10-50% EtOAc:Hexanes) to afford a white solid. (0.161 g, 0.731 mmol, 80%) **[α]$^{26}_{D}$** = -17.1° (c = 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ7.44-7.34 (m, 5H), 5.23 (d, J = 2.5 Hz, 1H), 5.20 (td, J = 1.0, 5.0 Hz, 1H), 5.07 (d, J = 5.0 Hz, 1H), 4.64 (app t, J = 2.0 Hz, 1H), 2.86 (dd, J = 6.0, 18.8 Hz, 1H), 2.79 (d , J = 18.5 Hz, 1H), 1.36 (d, J = 2.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.4, 134.2, 128.9, 128.6, 126.6, 87.2, 82.8, 77.1, 75.8, 36.0; **IR** (neat, cm^{-1}) 3948.3, 2975.6, 2948.6, 2923.6, 2858.0, 1766.5, 1496.49, 1454.1; **HRMS** (ESI) m/z calculated for $C_{12}H_{12}O_4Na$ $[M+Na]^+$: 243.0645; found 243.0633

2.5 References

[40] A portion of this work was summarized in a previous publication: Dustin J. Covell and M. Christina White *Angew. Chem. Int. Ed.* **2008**, *47*, 6448 - 6451.

[41] General C—H oxidation, aminations, alkylations: (a) Muller, P.; Fruit, C. *Chem. Rev*. **2003**, *103*, 2905. (b) Espino, C. G.; DuBois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 379. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439, and references therein. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (e) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (f) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (g) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (h) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090. (i) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015. (j) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (k) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (l) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566. (m) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.Eur. J.* **2010**, *16*, 2654. (n) Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W. *Science* **2006**, *312*, 1941.

[42] Pd-catalyzed allylic C—H oxidations: (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (b) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (c) Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032. (d) Delcamp, J. H.; White, M. C. *J. Am.Chem. Soc.* **2006**, *128*, 15076. (e) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448. (f) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew.Chem., Int. Ed.* **2006**, *45*, 481. (g) Pilarski, L. T.; Selander, N.; Bose, D.; Szabo, K. J. *Org. Lett.* **2009**, *11*, 5518. (h) Lin, B.-L.; Labinger, J. A.; Bercaw, J. E. *Can. J. Chem.* **2009**, *87*, 264. (i) Thiery, E.; Aouf, C.; Belloy, J.; Harakat, D.; Le Bras, J.; Muzart, J. *J. Org. Chem.* **2010**, *75*, 1771. (j) Henderson, W. H.; Check, C. T.; Proust, N.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 824.

[43] Pd-catalyzed allylic C—H aminations: (a) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584. (b) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274. (c) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316. (d) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733. (e) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707. (f) Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11701. (g) Nahra, F.; Liron, F.; Prestat, G.; Mealli, C.; Messaoudi, A.; Poli, G. *Chem.sEur. J.* **2009**, *15*, 11078. (h) Shimizu, Y.; Obora, Y.; Ishii, Y. *Org. Lett.* **2010**, *12*, 1372.

[44] BQ-promoted inner-sphere reductive elimination of acetate from π-allyl-Pd in 1,4-diacetoxylations: Backvall, J.-E.; Bystroem, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619.

[45] (a) Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A. *Tetrahedron Lett.* **1995**, *36*, 1831 77-84% ee (44-64% yield), 4 equiv. SM. For Cu(bis-oxazoline)/*tert*-butyl *p*-nitroperbenzoate. (b) Andrus, M. B.; Zhou, Z. *J. Am. Chem. Soc.* **2002**, *124*, 8806 94-99% ee (13-44% yield), 5 equiv. SM. (c) Eames, J.; Watkinson, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 3567. (d) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845.

[46] For examples of asymmetric olefination of aldehydes, see: (a) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777. (b) Brubaker, J. D.; Myers, A. G. *Org. Lett.* **2007,** *9*, 3523 and references therein. For chiral pool starting material derivatization examples, see: (c) Sheddan, N. A.; Mulzer, J. *Org. Lett.* **2006**, *8*, 3101. (d) Ichikawa, Y.; Yamaoka, T.; Nakano, K.; Kotsuki, H.; *Org. Lett.* **2007**, *9*, 2989. For resolution examples, see: (e) Itoh, T.; Kudo, K.; Yokota, K.; Tanaka, N.; Hayase, S.; Renou, M. *Eur. J. Org. Chem.* **2004**, *2*, 406. (f) Chênevert, R.; Gravila, S.; Bolteb, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2081.

[47] For elegant metal catalyzed enantioselective routes to chiral allylic esters see: (a) Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005,** *127*, 2866. (b) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc.* **2006,** *128*, 15572.

[48] Interaction of the bis-sulfoxide ligand of **13** with $Pd(OAc)_2$ has not been observed (^{1}H NMR, IR, UV, MS). For evidence of a Pd(II)-benzoquinone complex see: (a) Albeniz, A. C.; Espinet, P.; Martin-Ruiz, B. *Chem. Eur. J.* **2001**, *7*, 2481. (b) Bäckvall, J. E.; Gogoll, A *Tetrahedron Lett.*, **1988**, *29*, 2243.

[49] (a) Tolman, C. A.; Seidel, W. C.; Druliner, J. D.; Domaille, P. J. *Organometallics* **1984**, *3*, 33. (b) Huang, J.; Haar, C. M.; Nolan, S. P.; Marcone, J. E.; Moloy, K. G. *Organometallics* **1999**, *18*, 297. (c) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734. (d) Ref. 43c.

[50] Commercial (*1R,2R*)-(-)-[1,2-cyclohexanediamino-N,N'-bis(3,5-di-*t*-butylsalicylidene)]Cr(III)Cl was used, either antipode is available.

[51] Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunga, M. *Tetrahedron Lett.* **1997**, *38*, 773.

[52] See Appendix A for a summary of catalysts and their results.

[53] See 45a-c. For Cu(*i*-p-pybox-diph)/*tert*-butylperbenzoate: (a) 27% ee (15% yield) for octene, 40% ee (28% yield) for allylbenzene, 10 equiv. SM: Ginotra, S. K.; Singh, V. K. *Tetrahedron* **2006,** *62***,** 3573. For Ru(porphyrin)/2,6-dichloropyridine *N*-oxide: (b) 12-76% ee (5-35% yield), 1 equiv. SM: Zhang, R.; Yu, W.; Che, C. *Tetrahedron: Asymmetry* **2005**, *16*, 3520. For $Se/K_2S_2O_8$: (c) 75% ee (23% yield) for β-methylstyrene, 1 equiv. SM: Wirth, T.; Häuptli, S.; Leuenberger, M. *Tetrahedron: Asymmetry* **1998**, *9*, 547. For Mn(salen)/iodosylbenzene: (d) 53-64% ee (19-29% yield), 1 equiv SM: Hamachi, K.; Irie, R.; Katsuki, T. *Tetrahedron Lett.*, **1996**, *37*, 4979. For Cu(bis-oxazoline)/*tert*-butylperbenzoate: (e) 30% ee (50% yield) for octene, 36% ee (34% yield) for allylbenzene, 5 equiv. SM: Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G. *Tetrahedron Lett.*, **1995** *36*, 2945. For Cu(proline)/*tert*-butylperbenzoate: (f) 10-54% ee (23-63% yield), 10 equiv. SM: Levina, A.; Muzart, J. *Tetrahedron: Asymmetry,* **1995**, *6*, 147. For Fe(porphyrin)/iodosylbenzene: (g) 40-72%ee (19-72% yield), 10 equiv. SM: Groves, J. T.; Viskif, P. *J. Org. Chem.* **1990**, *55*, 3628.

[54] (a) El-Qisiari, A. K.; Qaseer, H. A.; Henry, P. M.; B.-F. Shi, *Tetrahedron Lett.*, **2002**, 43, 4229. (b) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 4882.

[55] Significantly, Cr(salen) complexes are known to achieve asymmetric catalysis by both activating aldehyde electrophiles in hetero-Diels-Alder reactions as well as activating carboxylic acid nucleophiles and epoxide electrophiles in epoxide ring opening reactions: (a) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403. (b) ref. 54

[56] Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron: Asymmetry* **1997**, *8*, 155.

[57] For examples of asymmetric olefination of aldehydes, see: (a) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777. (b) Brubaker, J. D.; Myers, A. G. *Org. Lett.* **2007,** *9*, 3523 and references therein (c) Hargadena, G. C.; Guiry, P. J. *Adv. Synth. Catal.*, **2007**, *349*, 2407 and references therein. For chiral pool starting material derivatization: (d) Sheddan, N. A.; Mulzer, J. *Org. Lett.*, **2006**, *8*, 3101. (e) Ichikawa, Y.; Yamaoka, T.; Nakano, K.; Kotsuki, H.; *Org. Lett.* **2007**, *9*, 2989. For asymmetric epoxidation based examples, see: (f) Babu, K. V.; Sharma , G. V. M. *Tetrahedron: Asymmetery* **2008**, *19*, 577. (g) Yadav, J. S. and Srihari, P. *Tetrahedron: Asymmetery* **2004**, *15*, 81. For resolution examples, see: (h) Itoh, T.; Kudo, K.; Yokota, K.; Tanaka, N.; Hayase, S.; Renou, M.; *Eur. J. Org. Chem.* **2004**, *2*, 406. (i) Chênevert, R.; Gravila, S.; Bolteb, J.; *Tetrahedron: Asymmetery* **2005**, *16*, 2081.

[58] For elegant metal catalyzed enantioselective routes to chiral allylic esters see: a) Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005,** *127*, 2866. (b) Geurts, K.; Fletcher, S. P.; Feringa, B. L.; *J. Am. Chem. Soc.* **2006,** *128*, 15572.

[62] Streamlining synthesis via late-stage C—H oxidation: (a) For first explicit demonstration of this concept, see: Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223. (b) Covell, D. J.; Vermeulen, N. A.; White, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 8217. (c) Stang, E. M.; White, M. C. *Nat. Chem.* **2009**, *1*, 547. For excellent reviews, see: (d) Hoffman, R. W. *Synthesis* **2006**, *21*, 3531. (e) Hoffman, R. W. In *Elements of Synthesis Planning*; Springer: Heidelberg, **2009**. For some elegant examples of late stage C—H hydroxylation and amination, see: (f) Wender, P. A.; Hilinski, M. K.; Mayweg, A. V. W. *Org. Lett.* **2005**, *7*, 79. (g) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.

[60] Yadav, J. S.; Chetia, L *Org. Lett.*, **2007**, *9*, 4587.

[61] Boren, L.; Martin-Matute, B.; Xu, Y.; Cordova, A.; Backvall, J. E. *Chem. Eur. J.* **2006**, *12*, 225.

[62] Yadav, J. S.; Joyasawal, S; Duttab, S. K.; Kunwarb, A. C.; *Tetrahedron Lett.*, **2007**, *48*, 5335.

[63] Yokokawa, Y.; Kobayashi, K.; Yokoyama, M.; Yamamuray, S. *Chem. Lett.*, **2003**, *32*, 844.

[64] Singh, S.; Singh, O. V.; Han, H.; *Tetrahedron Lett.*, **2007**, *48*, 8270.

[65] Isolation: (a) Cao, S. G.; Wu, X. H.; Sim, K. Y.; Tan, B. K. H.; Pereira, J. T.; Gog, S.-H. *Tetrahedron* **1998**, *54*, 2143. Synthesis: (b) Babjak, M.; Kapitan, P.; Gracza, T. *Tetrahedron Lett.* **2002**, *43*, 6983. (c) Yoda, H.; Nakaseko, Y.; Takabe, K. *Synlett* **2002**, *9*, 1532. (d) Murga, J.; Ruiz, P.; Falomir, E.; Carda, M.; Peris, G.; Marco, J. A. *J. Org. Chem.* **2004**, *69*, 1987. (e) Yadav, J. S.; Raju, A. R.; Rao, P. P.; Rajaiah, G. *Tetrahedron: Asymmetery* **2005**, *16*, 3283. (f) Babjak, M.; Kapita´n, P.; Gracza, T. *Tetrahedron* **2005**, *61*, 2471. (g) Carreno, M. C.; Hernandez-Torres, G.; Urbano, A.; Colobert, F. *Org. Lett.* **2005**, *7*, 5517. (h) Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2006**, *71*, 3643. (i) Ghosh, S.; Rao, C. N.; Dutta, S. K. *Synlett* **2007**, *9*, 1464. (j) Kang, B.; Chang, S.; Decker, S.; Britton, R.; *Org. Lett.* **2010**, *12*, 1716. (k) Brichacek, M.; Batory, L. A.; Njardarson, J. T.; *Angew. Chem. Int. Ed.* **2010**, 49, 1648.

[66] For examples of cooperative heterobimetallic catalysis see: (a) Ref. 45b. (b) *Multimetallic Catalysts in Organic Synthesis* (Eds: M. Shibasaki, Y. Yamamoto), Wiley-VCH, New York, **2004** (Chapter 1). For examples from asymmetric catalysis see: (c) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc*, **1992**, *114*, 4418. (d) Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309. (e) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928.

[67] Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006,** *128*, 15076.

[68] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[69] Kowalczyk, R.; Sidorowicz, L.; Skarzewsk, J. *Tetrahedron: Asymmetry* **2007**, *18*, 2581.

[70] Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004,** *126*, 4800.

[71] Jarvo, R. E.; Lawrence, B. M.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6043.

[72] Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2398.

[73] Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

[74] Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773.

[75] Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998,** *63*, 403.

[76] (a) Baldwin, J. E.; Bonacorsi Jr., S. J.; Burrell, R. C. *J. Org. Chem.* **1998,** *63*, 4721. (b) Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 3120.

[77] Orain, D.; Guillemin, J. *J. Org. Chem.* **1999,** *64*, 3563.

[78] Trost, B. M.; Metzner, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3572.

[79] Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron: Asymmetry* **1997**, *8*, 155.

[80] Jacobsen, M.; Redfern, R. E.; Jones, W. A.; Aldridge, M. H. *Science*, **1970**, *170*, 543.

[81] Boren, L.; Martin-Matute, B.; Xu, Y.; Cordova, A.; Backvall, J.-E. *Chem. Eur. J.* **2006**, *12*, 225.

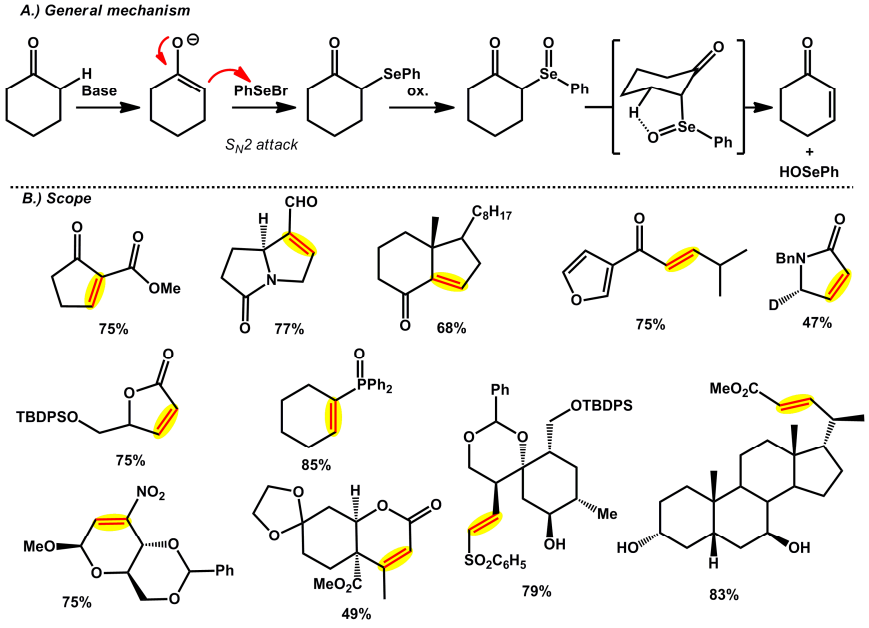
[82] Wang, Y. F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C. H. *J. Am. Chem. Soc.* **1998,** *110*, 7200.

Palladium Catalyzed Dehydrogenation of Unactivated Carbonyl Compounds

3.1. Introduction

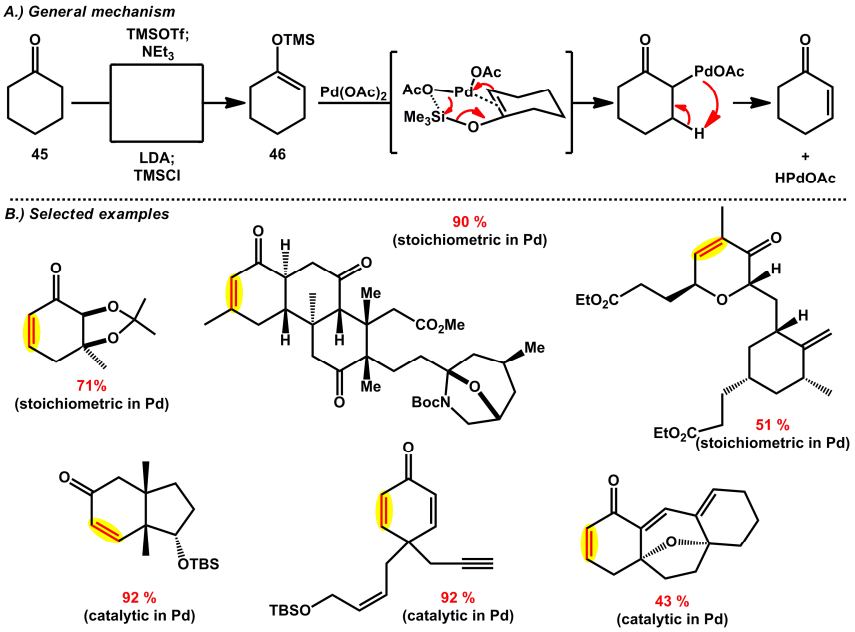
A fundamental component of organic synthetic strategy is the union of small fragments through the attack of a nucleophile on an electrophile. This concept is so general that methods which generate electrophilic or nucleophilic sites for further reaction are of particular importance for molecular construction. One versatile class of electrophiles are α,β-unsaturated carbonyl compounds. These structures are particularly useful due to the ease with which they can be further elaborated through a variety of selective transformations.[83] Additionally, modern advances have enabled many of these methods to be carried out stereoselectively. A number of highly useful methods for making α,β-unsaturated carbonyl compounds from two fragments have been developed including carbonyl annulations[83g-f] and condensations,[84] carbanion based strategies (Wittig and Horner-Wadsworth-Emmons reactions),[85] and transition metal catalyzed processes (olefin metathesis[86] and Heck reactions).[83r-s] While these reactions are effective for forming α,β-unsaturated carbonyl compounds, accessing this functionality directly from the parent carbonyl compound is often desired. In these cases, organic chemists turn to dehydrogenation reactions.

Figure 3.1. General mechanism and scope of selenium based dehydrogenations



Converting a carbonyl to its α,β-unsaturated homolog can be accomplished through several strategies. The most frequently employed are two step processes that first install an activating group, and then subsequently convert the "activated" carbonyl to its unsaturated form. For example, a ketone can be deprotonated to form an enolate, be transformed into an α-halocarbonyl by trapping with an electrophilic halogen, and then have its halide eliminated via a subsequent E2 mechanism to give an enone.[87] More commonly, selenium is used as an enolate trapping reagent because the resulting selenide undergoes facile dehydroselenation after a mild oxidation step (Figure 3.1A). Selenium has been used to effect dehydrogenation on a wide range of substrates in moderate to excellent yield (Figure 3.1B).[88] However, these methods require the use of stoichiometric amounts of the "activating-agent" and multiple steps under a variety of reaction conditions (*e.g.* basic, oxidative, thermal, etc.). Additionally, the highly reactive nature of the "activated" intermediates often leads to a variety of undesirable side reactions, diminishing overall yield and complicating product isolation.[89]

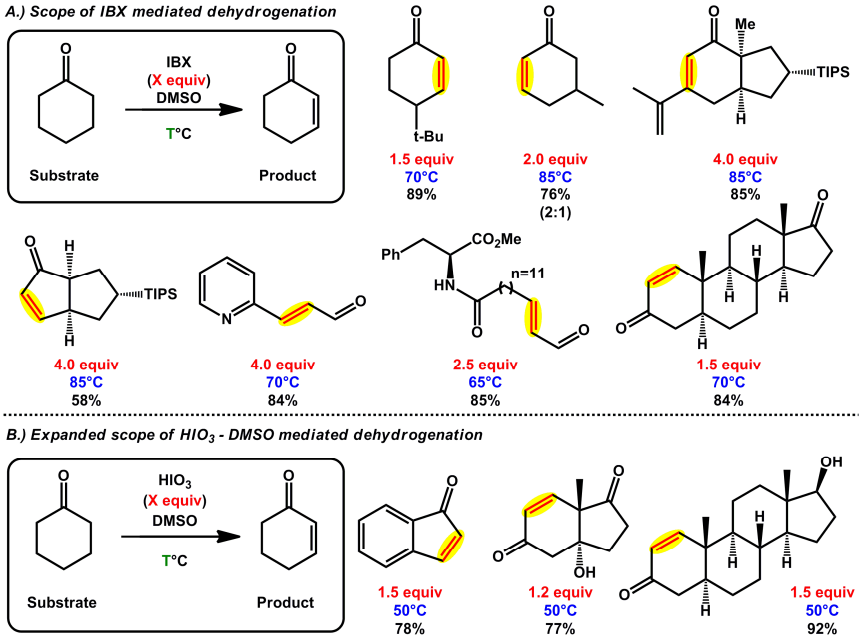
Figure 3.2. General mechanism and scope of palladium based oxidation of silylated carbonyl compounds



The palladium-based oxidation of silylated carbonyl compounds such as **46** (Figure 3.2A), or Saegusa oxidation,[90] is another common "pre-activation" approach. Attack of the silylated carbonyl compound on palladium forms a transient Pd-enolate intermediate that then β-hydride eliminates to give the desired unsaturated product (Figure 3.2A). Protonolysis of the Pd-enolate intermediate prior to elimination is the most significant challenge for this reaction manifold, as the resulting carbonyl compound is unreactive. However, when carried out effectively,

this mild approach using stoichiometric or superstoichiometric quantities of palladium affords good yields on a variety of substrate classes (eg. silylated esters, ketones, aldehydes) and exhibits excellent functional group tolerance (Figure 3.2B). Furthermore, several catalytic variants of this transformation have been developed and optimized, though their scope has proven to be more limited, necessitating the continued use of stoichiometric metal.[91,92]

Figure 3.3. Scope of hypervalent iodine dehydrogenation of unactivated carbonyl compounds

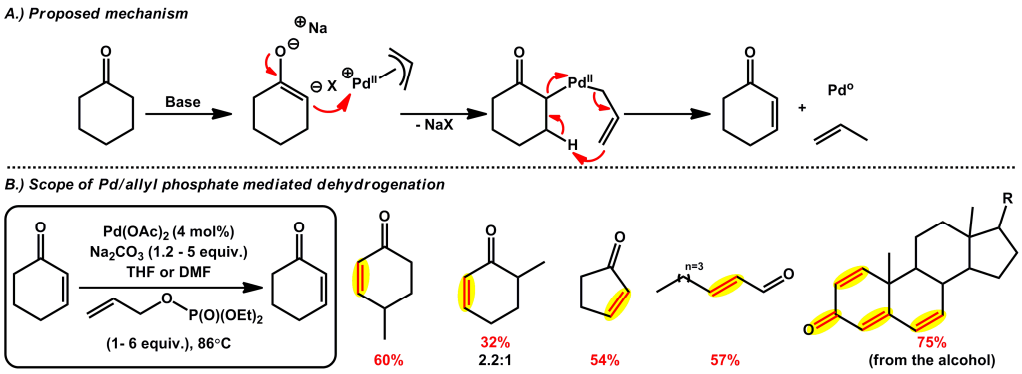


Direct conversion of carbonyls into α,β-unsaturated carbonyls, without an activating step, is much less developed. Many of the reagents previously described for multi-step dehydrogenations can be modified to effect a single pot transformation through a series of equilibrating intermediates. However, these systems have not shown sufficient generality to be widely used, owing in part to the challenge of driving the reaction from a carbonyl toward its more reactive unsaturated homolog under thermodynamic conditions.[88]

In 2000, Nicoloau and co-workers disclosed that hypervalent iodine, known to be an efficient oxidant for alcohols and silylated carbonyls, was capable of oxidizing carbonyls to their α,β-unsaturated form without the need for preactivation. In a series of reports the group demonstrated that a wide variety of aldehydes, ketoesters, and cyclic- and acyclic- ketones could be smoothly oxidized by 1-hydroxy-1,2-benziodoxal-3(1H)-one-1-oxide (IBX)[93] in dimethyl sulfoxide (DMSO) solvent in good to excellent yield with good functional group tolerance (Figure 3.3A). Mechanistic studies identified that this reaction most likely proceeds through attack of a transient enol on iodine(V) followed by sequential single electron transfer steps to give the desired product, iodine(III), and water.[94]

Building off of this mechanistic study, Nicolaou identified in 2002 that iodic acid (HIO_3) could serve as an alternative to IBX for dehydrogenation, cleanly oxidizing cyclic- and acyclic-ketones or aldehydes even in the presence of unprotected alcohol functionality (Figure 3.3B).[95] Promisingly, a catalytic hypervalent iodine dehydrogenation of cyclic ketones, using Oxone© as a terminal oxidant, was reported in 2008,[96] though its scope has yet to be thoroughly examined.

Figure 3.4. Proposed mechanism and scope of palladium catalyzed dehydrogenation of unactivated carbonyl compounds under basic conditions

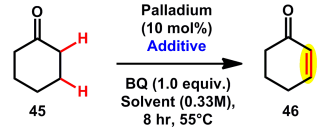


Oxidation of unactivated ketones using palladium has been extensively researched,[97] though success thus far for catalytic systems has been limited to only a few simple substrates (Figure 3.4). The systems developed to date suffer from poor conversion, commonly use substrate in solvent quantities, and often make mixtures of products due to over-oxidation. In reviewing this literature, I identified that most of the systems explored thus far have used high temperatures, strongly coordinating ligands, and/or basic reaction conditions. If one views the dehydrogenation transformation as two sequential C—H activations, these types of reaction conditions stand in stark opposition to the electrophilic conditions typically employed.[98] In particular, for palladium catalyzed C—H activation, weakly coordinating sulfoxide ligands and acidic conditions have been used to mildly activate allylic C—H bonds. [99,100] If similar conditions could be found to activate the α-carbonyl C—H bond selectively, subsequent β-hydride elimination would generate the desired unsaturated products. Furthermore, the broad scope and functional group tolerance of electrophilic palladium based C—H oxidations suggests that a system using this approach may overcome the substrate limitations of previously reported palladium catalyzed dehydrogenations.

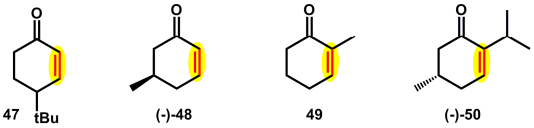
3.2. Results and Discussion

3.2.1 Discovery, Optimization, and Scope

Table 3.1. Discovery and optimization of Pd catalyzed dehydrogenation of unactivated carbonyl compounds under acidic conditions



Entry [a]	Palladium	Solvent	Additive	Conv. (%)	Yield (%)
1	$Pd(OAc)_2$- PhBS	THF	-	2	2
2	$Pd(OAc)_2$	DMSO	-	1	0
3	$Pd(OAc)_2$- PhBS	THF	CF_3CO_2H [b]	37	18
4	$Pd(OAc)_2$	DMSO	CF_3CO_2H [b]	69	54
5	$Pd(TFA)_2$	DMSO	-	37	16
6	$Pd(CH_3CN)_4(BF_4)_2$	DMSO	-	81	58
7	$Pd(CH_3CN)_4(BF_4)_2$	DMSO	*p*-$NO_2C_6H_4CO_2H$ [c]	82	72
8	$Pd(CH_3CN)_4(BF_4)_2$	DMSO	H_3PO_4 [b]	98	89



47	(-)-48	49	(-)-50
85% [d,e]	78% [d] 3.0:1	66% [d] 3.3:1	73% [e,f] 5.3:1

[a]Yields, conversions, and regioselectivity determined by gas chromatographic analysis using response factors from authentic samples and versus an internal nitrobenzene standard. [b]0.5 equiv. [c]1.0 equiv. [d]Yields and selectivities given are using conditions from entry 8 above [e]isolated yield of pure compound [f]1.2 equiv. BQ, 48 hrs. BQ = 1,4-benzoquinone, PhBS = 1,2-Bis-phenylsulfinylethane, TFA = Trifluoroacetate

I began my search for a more general palladium catalyzed dehydrogenation method by evaluating the palladium/sulfoxide combinations previously found to be effective for allylic C—H activation, namely $Pd(OAc)_2$-DMSO and $Pd(OAc)_2$-1,2-Bis-(phenylsulfinyl)ethane (PhBS). Not surprisingly, given the tolerance of carbonyl functionality in the previously disclosed allylic C—H activation reactions,[93] no dehydrogenation was observed (Table 3.1, entries 1 & 2). After screening a variety of additives, I first observed significant levels of the desired dehydrogenation of **45** to enone **46** upon adding 0.5 equivalents of trifluoracetic acid (Table 3.1, entries 3 & 4). Since exchange of carboxylates on palladium occurs readily, I reasoned that this addition may simply be making the more electrophilic palladium salt, $Pd(TFA)_2$. Dehydrogenation of **45** in the absence of acid additive was first

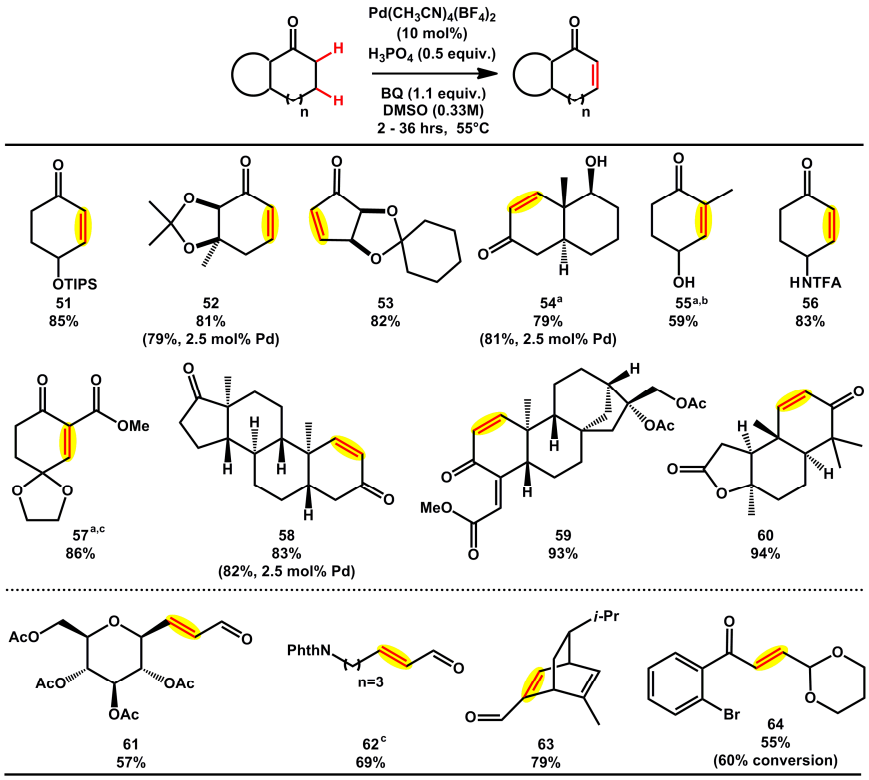
observed with $Pd(TFA)_2$ in DMSO (Table 3.1, entry 5). Extending this idea, the stable dicationic $Pd(CH_3CN)_4(BF_4)_2$ showed a marked improvement for dehydrogenation (Table 3.1, entry 6). Noting that acid had previously improved the efficiency of dehydrogenation (Table 3.1, entry 4 vs. 5), I evaluated a variety of acidic additives and found that mild acids such as *p*-nitrobenzoic acid and phosphoric acid were optimal. (Table 3.1, entries 7 & 8).

I next evaluated a variety of substituted cyclohexanones (Table 3.1, **47**-**50**) under the optimized conditions to determine the selectivity of this reaction. 4-*t*-Butylcyclohexanone was smoothly dehydrogenated to give product **47** in 85% isolated yield. *β*-Substituted (*R*)-3-methylcyclohexanone afforded a 78% yield of a 3.0:1 mixture of dehydrogenated products with preference for forming the less substituted enone **48**. Importantly, the major product was isolated and the stereocenter was determined to be unaffected by dehydrogenation. A "kinetic" dehydrogenation, giving the less substituted olefin, follows the general trend observed for direct dehydrogenation of unactivated carbonyls with palladium[97a] or IBX.[93] Additionally, the level of selectivity demonstrated by this reaction on this substrate is comparable to those previously reported (Figure 3.3).[97a] Interestingly, submitting 2-methylcyclohexanone to these reaction conditions resulted in a reversal of selectivity, affording a 3.3:1 mixture of products favoring the "thermodynamic" or more substituted olefin isomer (**49**) in 66% yield. To the best of my knowledge, this represents the first time this preference has been observed for any direct dehydrogenation system *vide supra* (Figure 3.4). Further, when examining a cyclohexanone with 2,5-substitution such as *L*-menthone, a noticeable reduction in reaction rate and increase in selectivity for formation of 2-substituted enone (-)-**50** was observed (73% isolated yield, 5.3:1 crude selectivity).[101]

Encouraged by the initial reactivity and selectivity of this dehydrogenation reaction, I next evaluated the substrate scope and functional group tolerance. I was delighted to find that cyclic- and acyclic-ketones, aldehydes, and keto-esters were all viable substrates for this reaction (Table 3.2). Additionally, a host of functionality was well tolerated, including acid sensitive groups (Table 3.2: **52**, **53**, **57**, **64**), common alcohol protecting groups (Table 3.2: **51**, **59**, **61)**, protected nitrogen functionality (Table 3.2: **56** and **62**), aromatic halogens (Table 3.2: **64**) and even unprotected alcohols (Table 3.2: **54**, **55**). Furthermore, a series of substrates with multiple sites of potential reactivity indicated that a "hierarchy" of reactivity can be used to predict which carbonyl in a compound would preferentially react. Specifically, a cyclohexanone could be reacted over a cyclopentanone (Table 3.2: **58**), a ketone could be cleanly reacted in the presence of a lactone (Table 3.2: **60**), and a ketoester reacts more rapidly than a

ketone (**57**). Linear ketones are suitable substrates, though preliminary studies suggest they react much more slowly at 55°C (**64**). Aldehydes are excellent substrates for this reaction (Table 3.2: **61** – **63**), giving good yields even for substrates with significant steric crowding adjacent to the aldehyde (Table 3.2: **63**). Finally, the reaction times were found to be sufficiently short (average = 12 hr) to allow for dramatically lower palladium loadings (2.5 vs 10 mol%, Table 3.2: **52**, **54**, **58**).

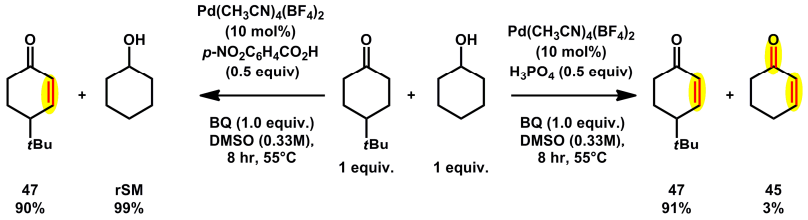
Table 3.2. Scope of Pd catalyzed dehydrogenation of unactivated carbonyls under acidic conditions



All reactions run on a 0.3 mmol scale unless otherwise noted. All yields reported are of isolated pure compound. [a]1.0 equiv. *p*-$NO_2C_6H_4CO_2H$ used as acid in reaction. [b]1.5 equiv. BQ [c]35°C. BQ = 1,4-benzoquinone

I performed a competition experiment with cyclohexanol and 4-*t*-butylcyclohexanone to further demonstrate the remarkable selectivity of this reaction for carbonyl over alcohol oxidation (Scheme 3.1, right). Subjecting one equivalent each of cyclohexanol and 4-*t*-butylcyclohexanone to the conditions described (*vide supra*, Table 3.1, entry 8) resulted in a 91% yield of **47** with only a 3% yield of **45** (resulting from alchol oxidation followed by dehydrogenation). Furthermore, even this trace alcohol oxidation could be eliminated by using *p*-nitrobenzoic acid instead of phosphoric acid as the acid for this transformation (Scheme 3.1, left).

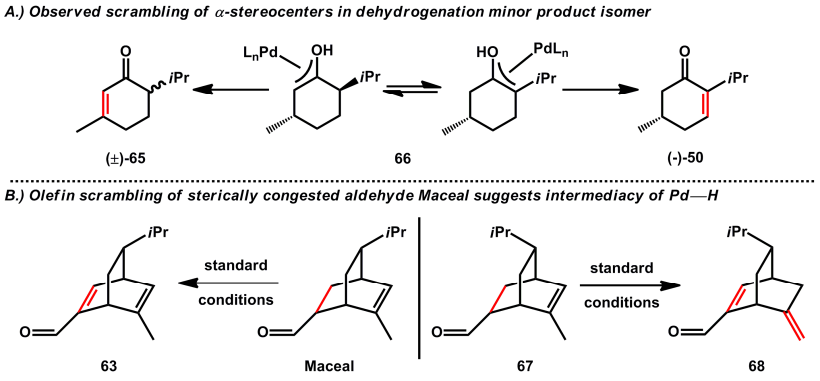
Scheme 3.1. Ketone vs. alcohol oxidation under acidic palladium catalyzed dehydrogenation



3.2.2 Mechanistic Observations

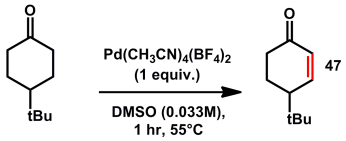
During the course of reaction development and exploration I made several observations that hinted this reaction was likely proceeding through a similar mechanism to that observed for stoichiometric palladium systems (i.e. formation of a Pd-enolate intermediate followed by β-hydride elimination). Firstly, the increased effectiveness of progressively more electrophilic palladium suggested to me that Pd-enolate formation may occur through attack of the carbonyls enol tautomer on the metal center. This type of reactivity is known to occur spontaneously in DMSO with strong halogen electrophiles such as NBS.[102] Secondly, the minor product of L-menthone dehydrogenation, **65,** has a racemic α-stereocenter (Figure 3.5A). This suggests that any Pd-enolate intermediate formed (**66)**, is long lived enough to sample both sides of the ketone, with hydride elimination occurring on the side of the carbonyl with the least steric hindrance at the β-position. However, it cannot be rigorously excluded that racemization of **65** occurs by epimerization after dehydrogenation. Thirdly, the likelihood of a Pd^{II}—H intermediate was demonstrated in dehydrogenation of commercially available Maceal, which comes as an approximately 85:15 mixture of separable isomers. Dehydrogenation of **67**, the minor isomer in the mixture, affords exclusively the unexpected olefin migration product **68**, which most likely results from a series of Pd—H insertions and β-hydride eliminations (Figure 3.5B).

Figure 3.5. Observations consistent with Pd-enolate and Pd—H species during dehydrogenation reaction



To probe the mechanism of this palladium catalyzed dehydrogenation reaction further, I evaluated the reaction under "mock catalytic"[103] conditions to determine the role of each of the components of the reaction during one catalytic cycle (Table 3.3). No dehydrogenation was observed in the absence of palladium (Table 3.3, entry 1), and baseline reactivity with $Pd(CH_3CN)_4(BF_4)$ in DMSO was sluggish (Table 3.3, entry 2). Benzoquinone (BQ) was found to have a modest accelerating effect on the rate of dehydrogenation, potentially by acting as a π-acidic ligand for palladium and further enhancing its electrophilic character (Table 3.3, entry 3). However, the most pronounced effect on rate was observed in the presence of phosphoric acid, which most likely increases the concentration of active enol tautomer (Table 3.3, entries 4 – 6, & 9). Significantly, reaction under rigorously anaerobic conditions showed a similar conversion, albeit a reduced yield, of dehydrogenation product **57** (Table 3.3, entry 6), suggesting that oxygen may play a role in the reaction but is not essential. Dramatically reduced reactivity was observed when the reaction was performed in THF rather than DMSO, though this shows sulfoxides are not an essential component of this reaction (Table 3.3, entry 7). Finally, unlike several of the C—H activation systems developed previously in the White lab, this reaction seems to have no real sensitivity to the steric environment presented by the quinone oxidant (Table 3.3, entries 3 & 4 vs. entries 8 & 9).

Table 3.3. Mechanistic exploration of palladium catalyzed dehydrogenation under "mock catalytic" conditions



Entry [a]	"additions" [b]	Conv.	Yield	k_{rel} [c]
1	BQ, H_3PO_4 [d]	5	0	-
2	-	12	5	1.0
3	BQ	25	19	2.9
4	BQ, H_3PO_4	87	82	8.2
5	H_3PO_4	82	79	8.2
6	H_3PO_4 [e]	85	61	-
7	BQ,H_3PO_4,THF [f]	51	41	5.7
8	2,6-DiMeBQ	26	23	4.0
9	2,6-DiMeBQ, H_3PO_4	84	78	7.6

[a]Conversion and yield determined in triplicate by GC versus an internal standard. [b]10 equiv. BQ, 10 equiv. 2,6-DiMeBQ or 5 equiv. H_3PO_4 were added when indicated. [c]Rates were determined by fitting a linear regression to GC analysis of timepoints taken at 15, 30, 45, and 60 min. [d]No $Pd(CH_3CN)_4(BF_4)_2$ [e]Run under anaerobic conditions. [f]THF as solvent (No DMSO)

Though no definitive mechanism has yet been determined for this direct dehydrogenation of carbonyls, a framework for the process is emerging. The acid additive, responsible for the most significant boost in reaction rate, most likely helps to promote an initial keto-enol tautomerization. Attack of this species on palladium forms a long lived Pd-enolate that subsequently undergoes β-hydride elimination to give a Pd^{II}—H. Conversion of this intermediate back to dicationic Pd^{II} by acid and benzoquinone would close the catalytic cycle. Furthermore, the lack of over oxidation in this system could be explained by the relative resistance of α,β-unsaturated carbonyls to undergo tautomerization.

3.3 Conclusions

In conclusion, I have developed a novel catalytic palladium(II)-based method for the conversion of ketones, ketoesters, and aldehydes directly to their unsaturated homologs, without the need for prior activation of the carbonyl. Importantly, this reaction shows good to excellent reactivity for a number of substrates with a rather diverse array of functional groups. Additionally, reaction under the acidic conditions discovered here affords unprecedented selectivities for dehydrogenation of 2-substituted ketones and, for the first time in any catalytic dehydrogenation reaction, shows a remarkable selectivity for oxidation of carbonyls over alcohols.

Preliminary mechanistic studies suggest the reaction proceeds through a Pd-enolate intermediate that undergoes successive β-hydride elimination to give the desired unsaturated carbonyl compounds, and that the acid additive is a key promoter of the reaction, likely via *in situ* promotion of keto-enol tautomerization. Further mechanistic study is necessary to confirm this hypothesis. Finally, this work demonstrates that the electrophilic, acidic conditions so successful for mild allylic C—H activation may be more generally applicable to discovering new reactivity with palladium.

3.4 Experimental Section

General Information: All commercially obtained reagents were used as received unless otherwise specified; Pd sponge, nitrosonium tetrafluoroborate (Strem), $Pd(OAc)_2$ (Alfa Aesar), benzoquinone, cyclohexanone, 2-methylcyclohexanone, (R)-(+)-3-methylcyclohexanone, 4-*t*-butylcyclohexanone, trifluoroacetic acid, *p*-nitrobenzoic acid, (Aldrich), phosphoric acid (Fisher). A sample of Maceal as a mixture (~85:15) of isomers was obtained from

Vigon international and purified via SiO_2 chromatogrphy (1-5% Et_2O:petroleum ether). *L*-menthone was obtained as 85% pure from Acros and purified via SiO_2 (5-20% ethyl acetate:hexanes) prior to use. $Pd(OAc)_2$ and $Pd(CH_3CN)_4(BF_4)_2$ were stored in a glove box under an argon atmosphere and weighed out in the air prior to use. Commercially available $Pd(CH_3CN)_4(BF_4)_2$ and "White Catalyst" (1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate) from Aldrich were found to be equivalent to that prepared freshly by the published procedures.[104,105] Solvents DMSO and THF were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). All dehydrogenation reactions were run were run under air unless specifically mentioned. Achiral gas chromatographic (GC) analyses were performed on Agilent Technologies 6890N Series instrument equipped with FID detectors using a HP-5 (5%-Phenyl)-methylpolysiloxane column (30m, 0.32mm, 0.25μm). Chiral gas chromatographic (GC) analyses were performed on an Agilent Technologies 5890A Series instrument equipped with an FID detector using a J&W Scientific β-cyclodextrin column (30m, 0.25mm, 0.25μm). HPLC analysis was performed on an Agilent Technologies 1100 HPLC system with a model 1100 Quaternary Pump, Diode Array Detector, Thermostat, and Autosampler. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, potassium permanganate, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still *et al.*[106] using EM reagent silica gel 60 (230-400 mesh). ^1H NMR spectra were recorded on a Varian Unity 400 (400 MHz) or a Varian Unity 500 (500 MHz), or a Varian Unity Inova 500NB spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C- NMR spectra were recorded on a Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory.

General Procedure for Palladium Catalyzed Carbonyl Dehydrogenation: A vial (4 mL borosilicate) was charged with the following: $Pd(CH_3CN)_4(BF_4)_2$ (10 mol%, 0.03 mmol, 13.3 mg), 1,4-benzoquinone (1.1 equiv., 0.33 mmol, 35.7 mg), and a Teflon© stir bar. Substrate (0.3 mmol) and DMSO (0.33M, 0.9 mL) were added and the vial was briefly (~15 seconds) stirred at room temperature until the solvent became homogeneous. Phosphoric acid (0.15 mmol, 8.8 μL) was then added via syringe and the reaction transferred to a 55°C bath and carefully monitored

(TLC, GC, or NMR). Upon complete consumption of SM, the reaction was cooled to room temperature and transferred to a separatory funnel with ~3 mL CH_2Cl_2 and then diluted further with CH_2Cl_2 (200 mL). The organic layer was rinsed with sat. aq. $NaHCO_3$ (2 x 50 mL) and brine (1 x 50 mL). The combined aqueous layers were back extracted with CH_2Cl_2 (100 mL). The combined organic layers were dried ($MgSO_4$ or Na_2SO_4), filtered, and reduced *in vacuo*. The resulting product is generally a mixture of dehydrogenation products and trace residual quinone/dihydroquinone, which can be purified via SiO_2 chromatography to afford clean material from which the yield was determined (^{1}H NMR).

Procedure for Optimization Screen (Table 3.1, compound 45, entries 1-8): A vial (4 mL borosilicate) was charged with the following: $Pd(OAc)_2$-PhBs (vial 1 & 3)(10 mol%, 0.01 mmol, 5.0 mg), $Pd(OAc)_2$ (vial 2 & 4)(10 mol%, 0.01 mmol, 2.2 mg), $Pd(TFA)_2$ (vial 5)(10 mol%, 0.01 mmol, 3.3 mg), $Pd(CH_3CN)_4(BF_4)_2$ (vial 6 – 8)(10 mol %, 0.01 mmol, 4.4 mg), 1,4-benzoquinone (vial 1 - 8)(1.0 equiv., 0.10 mmol, 10.8 mg), *p*-nitrobenzoic acid (vial 7)(1.0 equiv., 0.1 mmol, 16.7 mg), and a Teflon© stir bar. Cyclohexanone (vial 1 – 8)(1 equiv., 0.1 mmol, 10.4 μL), nitrobenzene (vial 1 – 8)(internal GC standard, 40 mol %, 4.1 μL), and DMSO (vial 2 & 4 – 8)(0.33M, 0.3 mL) or THF (vial 1 & 3) (0.33M, 0.3 mL) were added and the vial was stirred briefly (~15 seconds) at room temperature until the solvent became homogeneous. Aliquots were taken from the vials (~10 μL filtered with Et_2O through a short pipette plug of silica), to determine GC initial ratios of cyclohexanone to nitrobenzene. Trifluoroacetic acid (vial 3 & 4)(0.5 equiv., 0.05 mmol, 3.8 μL) or phosphoric acid (vial 8)(0.5 equiv., 0.05 mmol, 2.9 μL) was then added via syringe, the reaction capped, and transferred to a 55°C bath and carefully monitored (GC). Aliquots were taken from each vial at 8 hours to determine GC yields. Response factors relative to cyclohexanone were determined for the authentic cyclohexenone standard. Results are reported as an average of at least three runs.

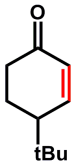
Procedure for "Mock Catalytic" Mechanistic Investigation Screen (Table 3.3): A vial (2 mL borosilicate) was charged with the following: $Pd(CH_3CN)_4(BF_4)_2$ (vial 2 - 9)(1 equiv., 0.01 mmol, 4.4 mg), 1,4-benzoquinone (vial 1,3 - 4, & 7)(10 equiv., 0.10 mmol, 10.8 mg), 4-t-butylcyclohexanone (vial 1 - 9)(1 equiv., 0.01 mmol, 1.5 mg), and a Teflon© stir bar. DMSO (vial 1 - 6, 8 - 9)(0.033M, 0.3 mL), THF (vial 7)(0.033M, 0.3 mL), nitrobenzene (vial 1 - 9)(internal GC standard, 4.0 equiv., 4.1 μL), and phosphoric acid (vial 1, 4 - 7, & 8)(5 equiv., 2.9 μL) were added

and the vial was stirred briefly (~15 seconds) at room temperature until the solvent became homogeneous. Aliquots were taken from the vials (~10 μL filtered with Et_2O through a short pipette plug of silica), to determine GC initial ratios of 4-*t*-butylcyclohexanone to nitrobenzene. The reaction was capped and transferred to a 55°C. Aliquots were taken from vials 1 - 5 & 7 - 9 at 15, 30, 45, and 60 minutes. Response factors relative to 4-*t*-butylcyclohexanone were determined from the authentic dehydrogenated standard. Results are reported as an average of at least three runs, with conversions and yields determined by GC as compared to the internal standard. Relative rates are based on the slope of a linear fit to the observed data for an experimental condition (Entry X) divided by that of the control (Entry 2). Vial 6 was set-up entirely in the glove box using rigorously degassed DMSO and run under an argon atmosphere. Time points were removed via syringe at t = 0 to determine initial ratios, and at t = 8 to determine conversion and yield via GC analysis.

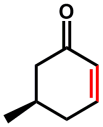
Procedure for Cyclohexanol vs. 4-*t*-Butylcyclohexanone Competition Experiments (Scheme 3.1): A vial (2 mL borosilicate) was charged with the following: $Pd(CH_3CN)_4(BF_4)_2$ (0.1 equiv., 0.01 mmol, 4.4 mg), 1,4-benzoquinone (1.0 equiv., 0.10 mmol, 10.8 mg), 4-*t*-butylcyclohexanone (1 equiv., 0.1 mmol, 15.4 mg), and a Teflon© stir bar. DMSO (0.33M, 0.3 mL), cyclohexanol (1 equiv., 10.6 μL), and nitrobenzene (internal GC standard, 4.0 equiv., 4.1 μL), and the vial was stirred briefly (~15 seconds) at room temperature until the solvent became homogeneous. Aliquots were taken from the vials (~10 μL filtered with Et_2O through a short pipette plug of silica), to determine GC initial ratios of cyclohexanol and 4-*t*-butylcyclohexanone to nitrobenzene. Phosphoric acid (0.5 equiv., 2.9 μL) or *p*-nitrobenzoic acid (1 equiv., 16.7 mg) was then added, the reaction capped, and transferred to a 55°C bath. Aliquots were taken from each vial at 8 hours to determine GC yields of 4-*t*-butylcyclohex-2-en-1-one, cyclohexanone, and cyclohex-2-en-1-one. Response factors relative to cyclohexanol, cyclohexanone, and 4-*t*-butylcyclohexanone were determined from authentic standards. Results are reported as an average of at least three runs.

General Procedure for Palladium Catalyzed Carbonyl Dehydrogenation (Table 3.1, substrates 47 -50; Table 3.2): A vial (4 mL borosilicate) was charged with the following: $Pd(CH_3CN)_4(BF_4)_2$ (10 mol%, 0.03 mmol, 13.3 mg), 1,4-benzoquinone (1.1 equiv., 0.33 mmol, 35.7 mg), and a Teflon© stir bar. Substrate (0.3 mmol) and DMSO (0.33M, 0.9 mL) were added and the vial was briefly (~15 seconds) stirred at room temperature until the solvent

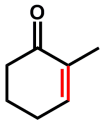
became homogeneous. Phosphoric acid (0.15 mmol, 8.8 μL) was then added via syringe and the reaction transferred to a 55°C bath and carefully monitored (TLC, GC, or NMR). Upon complete consumption of SM, the reaction was cooled to room temperature and transferred to a separatory funnel with ~3 mL CH_2Cl_2 and then diluted further with CH_2Cl_2 (200 mL). The organic layer was rinsed with sat. aq. $NaHCO_3$ (2 x 50 mL) and brine (1 x 50 mL). The combined aqueous layers were back extracted with CH_2Cl_2 (100 mL). The combined organic layers were dried ($MgSO_4$ or Na_2SO_4), filtered, and reduced *in vacuo.* The resulting product is generally a mixture of dehydrogenation products and trace residual quinone/hydroquinone, which can be purified via SiO_2 chromatography to afford clean material from which the yield was determined (^{1}H NMR).



4-(*Tert*-butyl)cyclohex-2-enone (47): Following the standard procedure afforded as a white solid: Run 1: 38.9 mg, 0.256 mmol, 85% yield, Run 2: 39.0 mg, 0.256 mmol, 85% yield; [**average yield: 85**%] which was spectroscopically identical to material previously reported in the literature[107]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.02 (dt, *J* = 10.4, 2.0 Hz, 1H), 6.04 (ddd, *J* = 10.4, 2.8, 1.0 Hz, 1H), 2.52 (dt, *J* = 16.6, 3.2 Hz, 1H), 2.34 (ddd, *J* = 16.6, 14.4, 5.0 Hz, 1H), 2.20 (ddt, *J* = 11.2, 4.8, 2.5 Hz, 1H), 2.15 – 2.05 (m, 1H), 1.81 – 1.68 (m, 1H), 0.98 (s, 9H) **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.5, 152.9, 130.0, 46.8, 37.8, 32.9, 27.3, 24.4.; **IR** (neat, cm^{-1}) 2958.2, 2931.3, 2871.5, 1689.3, 1469.5.

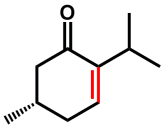


(*R*)-5-Methylcyclohex-2-enone (48): Reactions were run on 1.0 mmol scale instead of 0.3 mmol scale. Following the standard procedure afforded: Run 1: 84.9 mg, 0.771 mmol, 77% yield, Run 2: 86.0 mg, 0.781 mmol, 78% yield; Run 3: 85.7 mg, 0.778 mmol, 78% yield; [**average yield: 78** %]; which was spectroscopically identical to material previously reported in the literature[108]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.90 (ddd, *J* = 10.0, 5.0, 2.5 Hz, 1H), 5.90 (dd, *J* = 10.0, 1.0 Hz, 1H), 2.45–2.25 (m, 2H), 2.25–1.80 (m, 3H), 1.00 (d, *J* = 6.2 Hz, 3H).

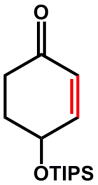


2-Methylcyclohex-2-enone (49): Reactions were run on 1.0 mmol scale instead of 0.3 mmol scale. Following the standard procedure afforded: Run 1: 71.1 mg, 0.645 mmol, 65% yield, Run 2: 71.7 mg, 0.651 mmol, 65% yield; Run 3: 73.5 mg, 0.667 mmol, 67% yield; [**average yield: 66**%]; which was spectroscopically identical to material previously reported in the literature [109]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.74

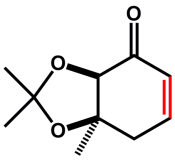
(td, *J* = 4.2, 1.4 Hz, 1H), 2.44 – 2.40 (m, 2H), 2.35 – 2.29 (m, 2H), 1.98 (dt, *J* = 12.4, 6.2 Hz, 2H), 1.77 (dd, *J* = 3.4, 1.8 Hz, 3H).



(*S*)-2-Isopropyl-5-methylcyclohex-2-enone ((-)-50): Following the standard procedure afforded: Run 1: 32.8 mg, 0.216 mmol, 72% yield, Run 2: 34.0 mg, 0.234 mmol, 75% yield; Run 3: 32.6 mg, 0.214 mmol, 71% yield; [**average yield: 73**%]; which was spectroscopically identical to material previously reported in the literature[110]; **$[\alpha]^{25}_{D}$** = -75.3° (c = 1.0, $CHCl_3$)(lit. $[\alpha]^{20}_{D}$ = -76, c = 0.56, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.64 (dd, *J* = 5.4, 2.3 Hz, 1H), 2.91 – 2.81 (m, 1H), 2.53 – 2.46 (m, 1H), 2.42 (dt, *J* = 9.9, 5.2 Hz, 1H), 2.21 – 2.13 (m, 1H), 2.13 – 2.06 (m, 1H), 2.02 (dd, *J* = 18.0, 9.5 Hz, 1H), 1.04 (d, *J* = 6.3 Hz, 3H), 1.00 (dd, *J* = 6.9, 3.2 Hz, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.3, 145.3, 141.3, 47.0, 34.3, 30.4, 26.2, 22.0, 21.8, 21.2.; **IR** (neat, cm^{-1}) 3041.2, 2958.3, 2929.4, 2912.0, 2873.4, 2829.1, 1675.8, 1459.9; **HRMS** (ESI) m/z calculated for $C_{10}H_{17}O$ $[M]^+$: 153.1279; found 153.1279.

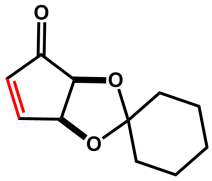


4-((Triisopropylsilyl)oxy)cyclohex-2-enone (51): Following the standard procedure afforded as a clear oil: Run 1: 67.7 mg, 0.252 mmol, 84% yield, Run 2: 68.9 mg, 0.257 mmol, 86% yield; Run 3: 69.0 mg, 0.257 mmol, 86% yield; [**average yield: 85** %]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.91 (ddd, *J* = 10.2, 2.3, 1.7 Hz, 1H), 5.93 (ddd, *J* = 10.3, 1.7, 1.0 Hz, 1H), 4.62 (ddt, *J* = 8.9, 4.5, 2.1 Hz, 1H), 2.59 (dt, *J* = 16.6, 4.4 Hz, 1H), 2.34 (ddd, *J* = 16.8, 12.6, 4.6 Hz, 1H), 2.28 (dddd, *J* = 11.1, 9.5, 4.7, 1.6 Hz, 1H), 2.04 (tdd, *J* = 12.8, 8.9, 4.2 Hz, 1H), 1.16 – 1.04 (m, 21H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 184.7, 154.0, 128.6, 67.0, 35.4, 33.1, 18.0, 17.7, 12.2.; **IR** (neat, cm^{-1}) 2942.9, 2892.7, 2865.7, 1691.3, 1463.7.

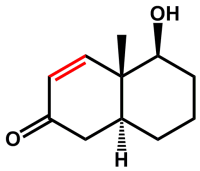


(**3aR,7aR)-2,2,7a-Trimethyl-7,7a-dihydrobenzo[1,3]dioxol-4(3aH)-one (52):** Following the standard procedure afforded as a clear oil: Run 1: 44.4 mg, 0.244 mmol, 81% yield, Run 2: 43.9 mg, 0.241 mmol, 80% yield; Run 3 (2.5 mol% $Pd(CH_3CN)_4(BF_4)_2$, 24 hr): 43.2 mg, 0.237 mmol, 79% yield; [**average yield: 81**%]; which was spectroscopically identical to material previously reported in the literature[111]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.92 (dt, *J* = 10.2, 4.2 Hz, 1H), 6.19 (dt, *J* = 10.2, 2.0 Hz, 1H), 4.04 (s, 1H), 2.84 (ddd, *J* = 19.3, 4.2, 2.1 Hz, 1H), 2.53 (ddd, *J* = 19.3, 4.3, 2.0 Hz, 1H), 1.46 (d, *J* = 7.1 Hz, 3H), 1.45 (s, 3H), 1.35 (d, *J* = 0.4 Hz, 3H).**^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.5, 148.1, 128.2, 109.8, 80.8, 80.6, 36.3, 28.1, 27.8,

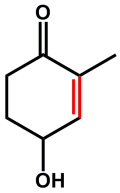
26.4.; **IR** (neat, cm^{-1}) 3039.3, 2987.2, 2935.1, 2873.4, 1683.6, 1456.0; **HRMS** (ESI) m/z calculated for $C_{10}H_{14}O_3Na$ $[M+Na]^+$ = 205.0841; found 205.0833.



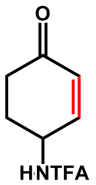
(3a'S, 6a'S) - 3a'H - Spiro[cyclohexane - 1,2' - cyclopenta[1,3]dioxol] - 4'(6a'H) - one (53): Following the standard procedure afforded: Run 1: 47.8 mg, 0.246 mmol, 82% yield, Run 2: 47.6 mg, 0.245 mmol, 82% yield; [**average yield: 82%**]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 5.9, 2.3 Hz, 1H), 6.20 (d, *J* = 5.9 Hz, 1H), 5.25 (dd, *J* = 5.4, 2.3 Hz, 1H), 4.46 (d, *J* = 5.4 Hz, 1H), 1.68 – 1.55 (m, 8H), 1.39 (m, 2H).



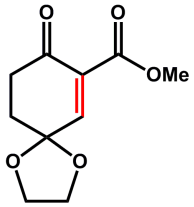
(4aR, 5S, 8aS)-5-Hydroxy-4a-methyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1H)-one (54): Following the standard procedure afforded: Run 1: 41.7 mg, 0.232 mmol, 77% yield, Run 2: 43.0 mg, 0.239 mmol, 80% yield; Run 3 (2.5 mol% $Pd(CH_3CN)_4(BF_4)_2$, 24 hr): 43.8 mg, 0.243 mmol, 81% yield; [**average yield: 79%**]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 10.0 Hz, 1H), 5.90 (dd, *J* = 10.0, 0.8 Hz, 1H), 3.46 (dt, *J* = 15.0, 5.0 Hz, 1H), 2.38 (dd, *J* = 17.5, 14.0 Hz, 1H), 2.28 (ddd, *J* = 17.5, 4.3, 0.8 Hz, 1H), 1.93 – 1.77 (m, 2H), 1.64 – 1.53 (m, 1H), 1.50 – 1.32 (m, 4H), 1.05 (s, 3H).



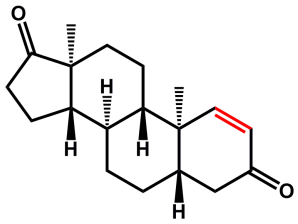
4-Hydroxy-2-methylcyclohex-2-enone (55): The polarity of this molecule necessitated an alternative work-up as compared to the standard procedure. Upon completion, the reaction was transferred to a separatory funnel with ~3 mL EtOAc, and then diluted with a further 200 mL EtOAc. The organic layer was washed once with sat. aq. $NaHSO_3$ (1 x 50 mL) and 5% aq. K_2CO_3 (2 x 50 mL). *Caution should be taken when combining aqueous layers as carbon dioxide is evolved.* The combined aqueous layers were back extracted with EtOAc (2 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and reduced *in vacuo.* SiO_2 chromatography afforded: Run 1: 19.7 mg, 0.156 mmol, 52% yield, Run 2: 20.8 mg, 0.165 mmol, 55% yield; Run 3: 21.4 mg, 0.170 mmol, 57% yield; [**average yield: 55%**]; **^{1}H NMR** (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69 (dt, *J* = 2.7, 1.4 Hz, 1H), 4.54 (s, 1H), 2.60 (dt, *J* = 17.8, 5.2 Hz, 1H), 2.33 (dddd, *J* = 11.2, 8.6, 6.4, 3.2 Hz, 2H), 2.04 (s, 3H), 1.95 (tdd, *J* = 17.0, 9.1, 3.4 Hz, 2H).



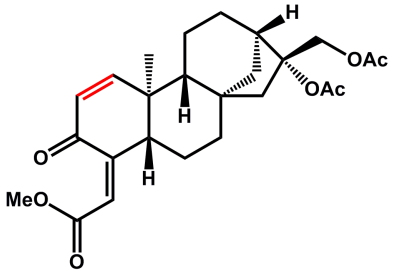
2,2,2-Trifluoro-N-(4-oxocyclohex-2-en-1-yl)acetamide (56): Following the standard procedure afforded: Run 1: 50.8 mg, 0.245 mmol, 82% yield, Run 2: 52.0 mg, 0.251 mmol, 84% yield; Run 3: 51.5 mg, 0.249 mmol, 83% yield; [**average yield: 83**%]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.78 (dt, *J* = 10.2, 2.0 Hz, 1H), 6.40 (bs, 1H), 6.13 (ddd, *J* = 10.2, 2.4, 0.8 Hz, 1H), 4.91 (dddd, *J* = 10.4, 7.7, 5.0, 2.4 Hz, 1H), 2.62 (dt, *J* = 17.0, 4.5 Hz, 1H), 2.56 – 2.48 (m, 1H), 2.43 (dtd, *J* = 12.8, 4.8, 3.2 Hz, 1H), 2.03 (tdd, *J* = 12.8, 10.7, 4.6 Hz, 1H).



Methyl 8-oxo-1,4-dioxaspiro[4.5]dec-6-ene-7-carboxylate (57): The standard procedure was modified in the following way: Instead of phosphoric acid, *p*-nitrobenzoic acid (1.0 equiv., 50 mg, 0.3 mmol) was used as a promoter. Additionally, the reaction was stirred at 35°C instead of 55°C. These modifications afforded: Run 1: 53.8 mg, 0.253 mmol, 85% yield, Run 2: 54.0 mg, 0.254 mmol, 85% yield; Run 3: 55.2 mg, 0.260 mmol, 87% yield; [**average yield: 86**%]; which was spectroscopically identical to material previously reported in the literature[112]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.15 (s, 1H), 4.11 – 4.02 (m, 4H), 3.82 (s, 3H), 2.75 – 2.68 (m, 2H), 2.23 (t, *J* = 6.6 Hz, 2H).

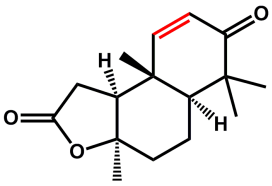


(**5S, 8R, 9S, 10R, 13S, 14S) - 10,13 - dimethyl - 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16-dodecahydro-3H-cyclopenta[a]phenanthrene-3,17(4H)-dione (58):** Following the standard procedure afforded: Run 1: 71.7 mg, 0.250 mmol, 83% yield, Run 2: 71.5 mg, 0.250 mmol, 83% yield; Run 3 (2.5 mol% $Pd(CH_3CN)_4(BF_4)_2$, 24 hr): 70.6 mg, 0.246 mmol, 82% yield; [**average yield:** 83%]; which was identical spectroscopically identical to material previously reported in the literature[113]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 10.2 Hz, 1H), 5.87 (d, *J* = 10.2 Hz, 1H), 2.47 (dd, *J* = 19.9, 9.2 Hz, 1H), 2.39 (dd, *J* = 16.0, 12.0 Hz, 1H), 2.25 (dd, *J* = 17.9, 3.9 Hz, 1H), 2.11 (dd, *J* = 18.9, 9.4 Hz, 1H), 2.01 – 1.81 (m, 4H), 1.66 (ddd, *J* = 22.6, 10.9, 3.3 Hz, 1H), 1.56 – 1.41 (m, 4H), 1.40 – 1.19 (m, 3H), 1.15 – 1.00 (m, 1H), 1.04 (s, 3H), 0.91 (s, 3H).

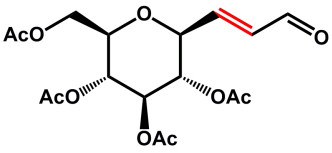


(*Z*) - methyl 2 - ((4aS, 6aS, 8R, 9R, 11aR, 11bS) - 8 - acetoxy - 8 - (acetoxymethyl) - 11b - methyl - 3 - oxo - 5, 6, 7, 8, 9, 10, 11, 11a - octahydro - 6a,9 - methanocyclohepta[a]naphthalen - 4(3H, 4aH, 11bH) - ylidene)acetate (59): Following the standard procedure afforded: Run 1:

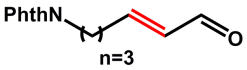
122.9 mg, 0.276 mmol, 92% yield, Run 2: 124.6 mg, 0.280 mmol, 93% yield; Run 3: 123.4 mg, 0.278 mmol, 93% yield; [**average yield: 93**%]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 10.1 Hz, 1H), 5.93 (d, *J* = 10.1 Hz, 1H), 5.83 (d, *J* = 2.2 Hz, 1H), 4.96 (d, *J* = 12.3 Hz, 1H), 4.47 (d, *J* = 12.3 Hz, 1H), 3.77 (s, 3H), 2.57 (d, *J* = 10.9 Hz, 2H), 2.08 (s, 3H), 2.04 (d, *J* = 15.7 Hz, 1H), 2.00 (s, 3H), 1.90 (d, *J* = 12.1 Hz, 1H), 1.86 – 1.52 (m, 12H), 1.46 (d, *J* = 7.7 Hz, 1H), 1.18 (s, 3H).



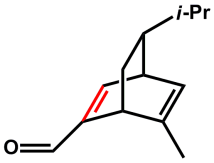
(3aR, 5aS, 9aR, 9bS) - 3a, 6, 6, 9a - tetramethyl - 1, 4, 5, 5a, 6, 9b - hexahydronaphtho[2, 1-b]furan-2, 7(3aH, 9aH) - dione (60): Following the standard procedure afforded: Run 1: 75.0 mg, 0.286 mmol, 95% yield, Run 2: 73.3 mg, 0.279 mmol, 93% yield; [**average yield: 94%**]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.84 (d, *J* = 10.0 Hz, 1H), 5.91 (d, *J* = 10.0 Hz, 1H), 2.60 (dd, *J* = 16.0, 14.6 Hz, 1H), 2.49 (dd, *J* = 16.1, 6.5 Hz, 1H), 2.23 (dd, *J* = 14.6, 6.5 Hz, 1H), 2.18 (dt, *J* = 12.0, 3.3 Hz, 1H), 1.98 – 1.89 (m, 1H), 1.84 – 1.70 (m, 1H), 1.68 – 1.53 (m, 2H), 1.42 (s, 3H), 1.19 (s, 3H), 1.19 (s, 3H), 1.12 (s, 3H).



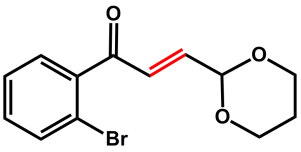
(2R, 3R, 4R, 5S, 6S)-2-(acetoxymethyl)-6-((E)-3-oxoprop-1-en-1-yl)tetrahydro-2H-pyran-3, 4, 5-triyl triacetate (61): This substrate was run on a 0.1 mmol scale rather than 0.3 mmol. Following the standard procedure afforded: Run 1: 22.0 mg, 0.569 mmol, 57% yield, Run 2: 22.5 mg, 0.058 mmol, 58% yield; [**average yield: 57**%]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.67 (d, *J* = 7.7 Hz, 1H), 6.89 (dd, *J* = 16.2, 3.6 Hz, 1H), 6.44 (ddd, *J* = 16.2, 7.7, 2.2 Hz, 1H), 5.22 (ddd, *J* = 18.0, 9.8, 7.2 Hz, 2H), 5.06 (app t, *J* = 10.0 Hz, 1H), 5.00 (ddd, *J* = 5.8, 3.5, 2.3 Hz, 1H), 4.26 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.11 (dd, *J* = 12.3, 2.4 Hz, 1H), 3.93 (ddd, *J* = 9.5, 5.4, 2.3 Hz, 1H), 2.11 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H).



(*E*) - 6 - (1,3-dioxoisoindolin - 2 - yl)hex - 2 - enal (62): Following the standard procedure afforded: Run 1: 46.3 mg, 0.200 mmol, 67% yield, Run 2: 48.7 mg, 0.210 mmol, 70% yield; [**average yield: 68**%]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.48 (d, *J* = 7.8 Hz, 1H), 7.86 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.1 Hz, 2H), 6.84 (dt, *J* = 15.6, 6.6 Hz, 1H), 6.15 (dd, *J* = 15.7, 7.8 Hz, 1H), 3.75 (t, *J* = 7.1 Hz, 2H), 2.41 (dd, *J* = 14.3, 7.4 Hz, 2H), 1.92 (dt, *J* = 14.4, 7.3 Hz, 2H).



(1R, 4S, 8S) - 8 - isopropyl - 6 - methylbicyclo[2.2.2]octa - 2,5 - diene - 2 - carbaldehyde (63): Following the standard procedure afforded: Run 1: 44.3 mg, 0.232 mmol, 78% yield, Run 2: 46.5 mg, 0.244 mmol, 81% yield; Run 3: 45.1 mg, 0.237 mmol, 79% yield; [**average yield: 79**%]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.26 (dd, *J* = 5.9, 1.6 Hz, 1H), 5.78 (d, *J* = 5.8 Hz, 1H), 4.14 (d, *J* = 6.0 Hz, 1H), 3.48 (dd, *J* = 5.9, 2.1 Hz, 1H), 1.83 (d, *J* = 1.2 Hz, 3H), 1.67 – 1.55 (m, 1H), 1.16 – 0.93 (m, 2H), 0.98 (d, *J* = 8.0 Hz, 3H), 1.16 – 0.93 (m, 1H), 0.81 (d, *J* = 6.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 187.9, 155.9, 151.6, 143.5, 124.0, 47.3, 44.3, 36.2, 33.8, 31.7, 21.8, 21.3, 19.0.



(*E*)-1-(2-bromophenyl)-3-(1,3-dioxan-2-yl)prop-2-en-1-one (63): Following the standard procedure afforded: Run 1: 49.2 mg, 0.165 mmol, 55% yield (36 mg rSM), Run 2: 48.7 mg, 0.163 mmol, 55% yield (34 mg rSM); [**average yield: 55%**]; **^{1}H NMR** (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (t, *J* = 7.8 Hz, 1H), 7.39 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.35 (td, *J* = 7.5, 1.1 Hz, 1H), 7.28 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.74 (d, *J* = 16.1 Hz, 1H), 6.44 (dd, *J* = 16.1, 3.2 Hz, 1H), 5.18 (d, *J* = 2.3 Hz, 1H), 4.18 (dd, *J* = 11.3, 4.6 Hz, 2H), 3.86 (t, *J* = 11.4 Hz, 2H), 2.18 – 1.98 (m, 2H).

3.5 References

[83] For examples of selective addition reactions, see: (a) Michael, A. J. *J. Prackt. Chem.* **1887**, *35*, 349. (b) Krause, N.; Hoffman-Roder, A. *Synthesis* **2001**, 171. (c) Kwiatkowski, P.; Dudzinski, K.; Łyzwa, D. *Org. Lett.*, ASAP **DOI:** 10.1021/ol201275h (d) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. (e) Hudelston, R. R.; Krische, M. J.*Synlett* **2003**, 12. (f) Shi, M.; Li, C.-Q.; Jiang, J.-K. *Tetrahedron* **2003**, *59*, 1181. For examples of annulations, see: (g) Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285. (h) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (i) Akiyanza, T.; Katoh, T.; Mori, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 4226. For examples of selective reduction, see: (j) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (k) Subba Rao, G. S. R. *Pure Appl. Chem.* **2003**, *75*, 1443. (l) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (m) Evans, D. A. *Science*, **1988**, *240*, 120.(n) Miyashita, A.; Yasuda, A.; Yakaya, H.; Toruimi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (o) Noyori, R. Kitamura, M.; Ohkuma, T. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5356. For other recent uses of unsaturaed carbonyls, see: (p) Rovis, T. *Chemtracts* **2003**, *16*, 542. (q) Feringa, B. L. *Transition Metals for Organic Synthesis* **1998**, *2*, 307. and references therein. (r) Lu, X.; Linm S. *J. Org. Chem.*, **2005**, *70*, 9651. (s) Le Bras, J.; Muzart, J. *Chem. Rev.*, **2011**, *111*,1170. (t) Krohnke, F. *Synthesis* **1976**, 1.

[84] (a) Heathcock, C. H. *Science* **1981**, *214*, 395. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

[85] (a) Horner, L.; Hoffman, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61. (b) Wadsworth, W. S.; Jr., Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. (c) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.(d) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Akai, T. *Tetrahedron Lett.* **1984**, *25*, 2183. (e) Edmonds, M.; Abell, A. *Modern Carbonyl Olefination* **2004**, 1.

[86] (a) Morgan, J. P.; Grubbs, R. H. *Org. Lett.*, **2000**, *2*, 3153 (b) Ferrie, L.; Bouzbouz, S.;Cossy, J. *Org. Lett.*, **2009**, *11*, 5446. (c)

[87] (a) Rinne, W. W.; Deutsch, H. R.; Bowman M. I.; Joffe, B. *J. Am. Chem. Soc.* **1950**, *72*, 5759. (b) Kaworth, W. N. *J . Chenr. Snc.* **1913**, *108* 1242. (c) Warnhoff, E. W.; Johnson W. S. *J. Am. Chem. Soc.*, **1953**, *75*, 494. (d) Miyagawa, T.; Nagai, K; Yamada, A.; Sugihara, Y.; Fukuda, T.; Fukuda, T.; Uchida, R.; Tomoda, H.; Omura, S.; Nagamitsu, T. *Org. Lett.* **2011**, *13* 1158.

[88] For an excellent review on selnium based methods, see: (a) Reich, H. J.; Wolfowitz, S. In *Organic Reactions* (Hoboken, NJ, United States) **1993**, *44*, (John Wiley & Sons, Inc.). For a few recent examples, see: (b) Peixoto, P. A.; Severin, R.; Tseng, C.-C.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3013. (c) Shi, J.; Manolikakes, G.; Yeh, C.-H.; Guerrero, C. A.; Shenvi, R. A.; Shigehisa, H.; Baran, P. S.; *J. Am. Chem. Soc.* **2011**, *133*, 8014. (d) Hayashida, J.; Rawal, V. H.; *Angew. Chem. Int. Ed.* **2008**, *47*, 4373.

[89] Selenide reaction in particular suffer from several significant side reactions. See ref. 88a for a discusion and techniques used to minimize these processes.

[90] (a) Bierling, B.; Kirschke, K.; Oberender, H.; Schulz, M. *J. Prakt. Chem.* **1972**, *314*, 170. (b) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. (c) Buckle, D. R.; Pinto, I. L. In *Comprehensive Organic Synthesis* **1991,** *7*, 119. (Pergamon, Oxford). (d) Heumann, A.,; Jens, K.-J.; Reglier, M. *Prog. Inorg. Chem.* **1994**, *42*, 483.

[91] (a) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. A.*Tetrehdron Lett.* **1995**, *36*, 2423. (b) Shimizu, I.; Minami, I.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 1797.

[92] For recent application of stoichiometric Saegusa oxidation, see: (a) Takahashi, K.; Watanabe, M.; Honda, T. *Angew. Chem. Int. Ed*. **2008**, *47*, 131 (b) Yokoe, H.; Mitsuhashi, C.; Matsuoka, Y.; Yoshimura, T.; Yoshida, M.; Shishido, K. *J. Am. Chem. Soc.* **2011**, *133*, 8854. (c) Petronijevic, F. R.; Wipf, P. *J. Am. Chem. Soc.* **2011**, *133*, 7704.

[93] (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran P. S. *J. Am. Chem. Soc.* **2000,** *122*, 7596-7597 (b)

[94] Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong Y.-L. *J. Am. Chem. Soc.* **2002**, *9*, 2245.

[95] Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1386.

[96] Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem.* Soc. **2009**, *131*, 251.

[97] For a recent review of palladium based oxidation of unativated ketones, see: (a) Muzart, J. *Eur. J. Org. Chem.* **2010**, 3779. For representative examples of these systems, see: (b) Y. W. Park, H. H. Oh, *Bull. Korean Chem. Soc.* **1997**, *18*, 1123. (c) Y. Shvo, A. H. I. Arisha, *J. Org. Chem.* **1998**, *63*, 5640. (d) J. Liu, J. Zhu, H. Jiang, W. Wang, J. Li, *Chem. Commun*. **2010**, 415.

[98] General C-H oxidation, aminations, alkylations: (a) Muller, P.; Fruit, C. *Chem. Rev*. **2003**, *103*, 2905. (b) Espino, C. G.; DuBois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 379. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439, and references therein. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev*. **2007**, *107*, 174. (e) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (f) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (g) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (h) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090. (i) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015. (j) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (k) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (l) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566. (m) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.Eur. J.* **2010**, *16*, 2654. (n) Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W. *Science* **2006**, *312*, 1941.

[99] Pd-catalyzed allylic C-H oxidations: (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (b) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (c) Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032. (d) Delcamp, J. H.; White, M. C. *J. Am.Chem. Soc.* **2006**, *128*, 15076. (e) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448. (f) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew.Chem., Int. Ed.* **2006**, *45*, 481. (g) Pilarski, L. T.; Selander, N.; Bose, D.; Szabo, K. J. *Org. Lett.* **2009**, *11*, 5518. (h) Lin, B.-L.; Labinger, J. A.; Bercaw, J. E. *Can. J. Chem.* **2009**, *87*, 264. (i) Thiery, E.; Aouf, C.; Belloy, J.; Harakat, D.; Le Bras, J.; Muzart, J. *J. Org. Chem.* **2010**, *75*, 1771. (j) Henderson, W. H.; Check, C. T.; Proust, N.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 824.

[100] Pd-catalyzed allylic C-H aminations: (a) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584. (b) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274. (c) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316. (d) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733. (e) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707. (f) Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11701. (g) Nahra, F.; Liron, F.; Prestat, G.; Mealli, C.; Messaoudi, A.; Poli, G. *Chem.sEur. J.* **2009**, *15*, 11078. (h) Shimizu, Y.; Obora, Y.; Ishii, Y. *Org. Lett.* **2010**, *12*, 1372.

[101] As with (*R*)-3-Methylcyclohexenone, the remote methyl stereocenter was unaffected by dehydrogenation in isolated (-)-**50**. See experimental section for details.

[102] Sreedhar, B.; Reddy, P. S.; Madhavi, M. *Synth. Comm.* **2007**, *37*, 4149 and references therein.

[103] Reaction run with 1 equiv. of 4-*t*-butylcyclohexanone, 1 equiv. of $Pd(CH_3CN)_4(BF_4)_2$, 5 equiv. of H_3PO_4, 10 equiv.of benzoquinone, nitrobenzene (internal GC standard, 4.0 equiv.), 0.033M in DMSO at 55°C and monitored via GC.

[104] Wayland B. B.; Schrammz, R. F. *Inorg. Chem.* **1969**, *4*, 971.

[105] Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* 2006, *128*, 15076.

[106] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, *43*, 2923.

[107] Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 251.

[108] Fleming, I.; Maiti, P.; Ramarao, C. *Org. Biomol. Chem.* **2003**, 1, 3989.

[109] Shvo, Y.; Arisha, A. H. I. *J. Org. Chem.* **1998**, *63*, 5640.

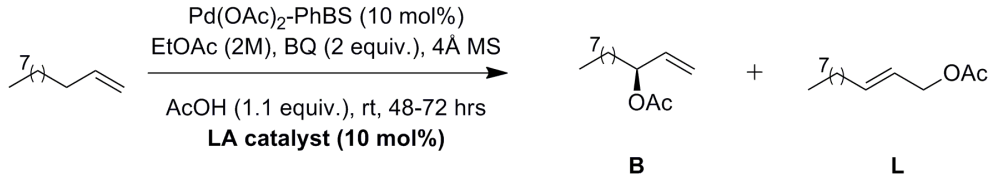
[110] Wang, P. Z.; Tu, Y. Q.; Yang, L.; Dong, C. Z.; Kitching, W. *Tetrahedron: Asymmetry* **1998**, *9*, 3789.

[111] Sha, Chin-Kang; Huang, Shih-Jung; Zhan, Zhuang-Ping Journal of Organic Chemistry, 67(3), 831-836; 2002

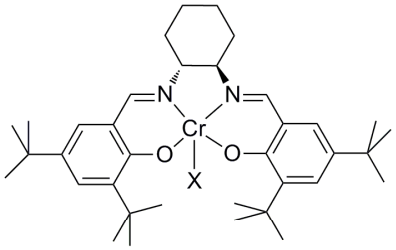
[112] Boyer, F.-D.; Descoins, C. L.; Thanh, G. V.; Descoins, C.; Prange, T.; Ducrot, P.-H. *Eur. J. Org. Chem.* **2003**, *7*, 1172.

[113] Zhang, H.; Qiu, Z. *Steroids* **2006**, *71*, 1088.

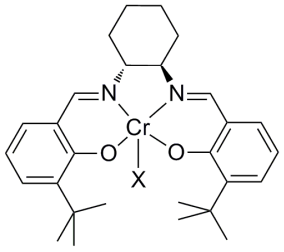
APPENDIX A: ***Chromium Lewis Acid Co-Catalysts Synthesized and Tested for Enantioselective Allylic C—H Oxidation***



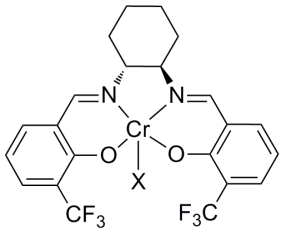
(Yield, B:L, and %ee are all determined via GC)



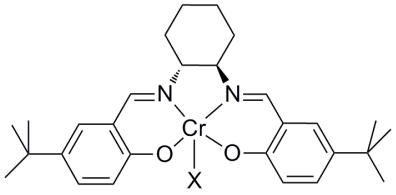
X	%Yield	B:L	%ee
Cl	90	1.7:1	41
BF_4	92	4.4:1	57
F	97	4.6:1	58
SbF_6	90	2.3:1	23
NO_3	94	4.2:1	52
OAc	61	3.1:1	27



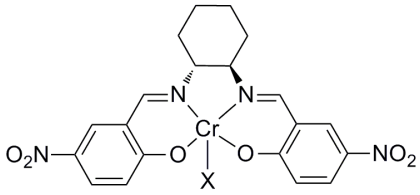
X	%Yield	B:L	%ee
Cl	41	2.2:1	17
BF_4	53	3.3:1	8
F	23	3.6:1	15



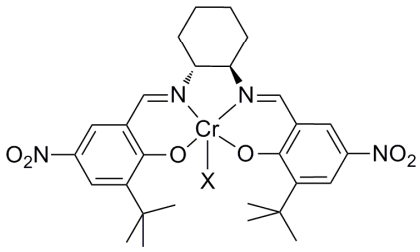
X	%Yield	B:L	%ee
Cl	36	1.6:1	0
BF_4	21	3.2:1	3
F	19	3.8:1	6
SbF_6	20	4.0:1	-1
NO_3	41	3.1:1	3



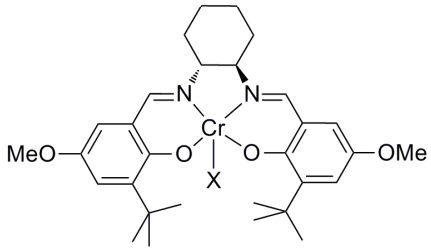
X	%Yield	B:L	%ee
Cl	62	1.3:1	-3



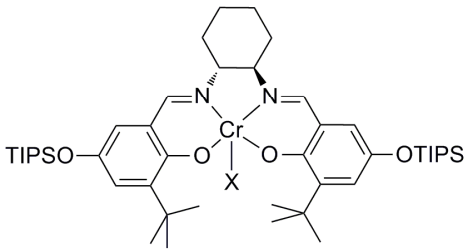
X	%Yield	B:L	%ee
Cl	38	6.1:1	5



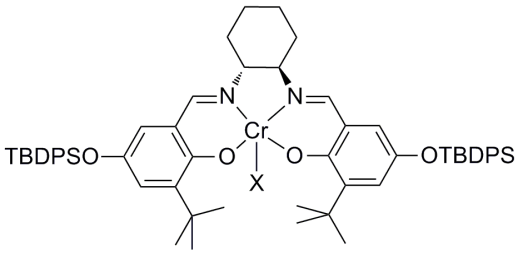
X	%Yield	B:L	%ee
Cl	37	6.4:1	1



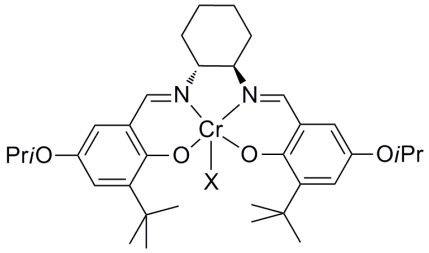
X	%Yield	B:L	%ee
Cl	71	1.8:1	21
BF_4	86	6.2:1	60
F	99	4.6:1	57
SbF_6	81	5.8:1	63
NO_3	75	1.3:1	48



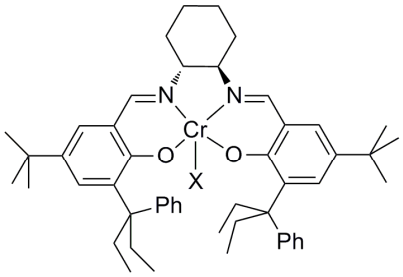
X	%Yield	B:L	%ee
Cl - MS	97	1.3:1	19
Cl	85	1.6:1	6
BF_4 - MS	57	2.4:1	6
BF_4	42	2.8:1	20
F - MS	88	2.8:1	23
F + MS	74	2.7:1	21



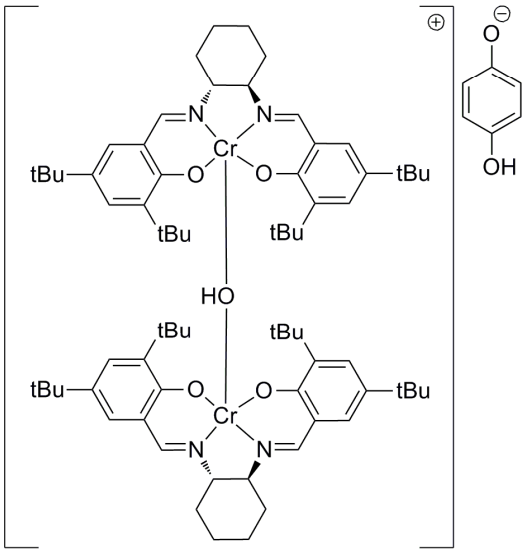
X	%Yield	B:L	%ee
Cl	11	4.5:1	9
BF_4	9	3.5:1	2
F	11	4.5:1	-4



X	%Yield	B:L	%ee
Cl	24	1:1.2	22
BF_4	74	4.3:1	49
F	65	4.0:1	40

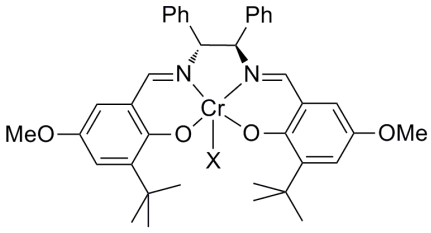


X	%Yield	B:L	%ee
Cl	89	1.1:1	27
BF_4	50	2.1:1	46
F	48	5.9:1	3
SbF_6	42	1.3:1	3
NO_3	79	1.8:1	26

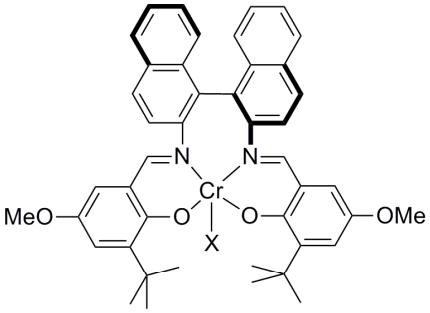


%Yield	B:L	%ee
92	5.2:1	56

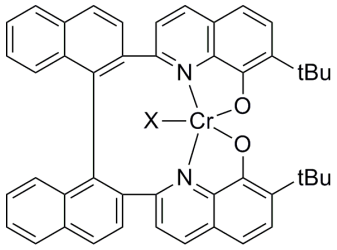
(5 mol% catalyst used)



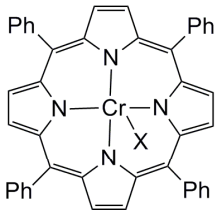
X	%Yield	B:L	%ee
Cl	73	1.5:1	3
BF_4	56	2.1:1	9
F	66	3.4:1	7



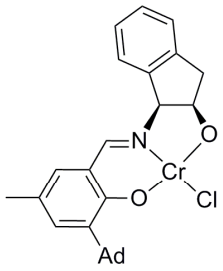
X	%Yield	B:L	%ee
Cl	16	3.0:1	-3
BF_4	26	5.5:1	0
F	53	9.6:1	-3



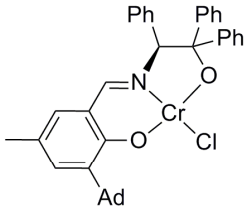
X	%Yield	B:L	%ee
Cl	5	1:1	0



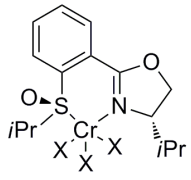
X	%Yield	B:L	%ee
Cl	39	5.9:1	-



X	%Yield	B:L	%ee
Cl (dimer)	31	1.8:1	-8
Cl (monomer)	3	2:1	-6



X	%Yield	B:L	%ee
Cl (dimer)	4	3:1	4
Cl (monomer)	-	-	-



X	%Yield	B:L	%ee
Cl	3	-	-