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Transition Metal Catalyzed Transformations of Strained Heterocycles

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Christian A. Malapit, Ph. D.

University of Connecticut, 2016

Heterocycles are present in more than half of organic compounds. For organic chemists, they are valued as synthetic targets or scaffolds to construct valuable products. For the past two decades, the Howell group has made contributions towards the synthesis and applications of 4-membered heterocyclic compounds, such as oxetanes and β-lactones. Most of the previously reported transformations that involve strained heterocyclic compounds rely on traditional methods in which rendering the reaction with good and predictable selectivity (regio-, chemo- and stereoselectivity) is challenging.

The works described took advantage of the intrinsic reactivity of strained heterocycles and combined that with the highly selective transformations promoted by transition metal (TM) catalysts. Three successful methodologies were developed. Chapter 1 describes the discovery and scope of a novel Pt-catalyzed expansion of spirocyclopropyl oxetanes to synthetically useful 3-methylenetetrahydrofurans. This unprecedented oxetane expansion was realized via cyclopropane activation under platinum catalysis. Mechanistic studies, through ^{13}C-labelling and ^{13}C-DEPT NMR analyses, suggested that the oxetane expansion was promoted by a regioselective carbon-carbon bond activation of cyclopropane with platinum.

Chapter 2 describes two transition metal catalyzed transformations of α-methylene-β-lactones. First is a Rh-catalyzed conjugate addition with aryl boronic acids to access various β-lactones. β-Lactones are highly privileged synthetic products and intermediates. They have been shown to elicit serine hydrolase inhibition. They are also used as intermediates to obtain difunctionalized acyclic compounds, and this was the goal in the next method. The second method developed involves a chemoselective opening of β-lactones to form β-hydroxy amides. Ring opening of β-lactones with several nucleophiles typically provide a mixture of two major products; opening via the (a) alkyl C–O bond, or (b) the acyl C–O bond. The selective ring-opening was realized via activation of acyl carbon-oxygen bond under palladium catalysis. Under the developed conditions, several β-lactones were selectively opened with various amine nucleophiles and gave β-hydroxy amides as sole product. This method was also translated to a Pd-catalyzed asymmetric kinetic resolution of racemic to enantioenriched β-lactones.

Transition Metal Catalyzed Transformations of Strained Heterocycles

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A Dissertation

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Approval Page

Doctor of Philosophy Dissertation

Transition Metal Catalyzed Transformations of Strained Heterocycles

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To Amy

and to my hometown, Bangui.

Acknowledgments

First of all, I would like to thank my advisor, Professor Amy Howell, for her exceptional guidance throughout my graduate school years. Her incredible motivation, valuable insights, and kind heart allowed me to hear and explore my voice as a scientist. Amy has been more than a research advisor to me. She was my mother, guardian, role model, and a great friend in the past five years. I thank Amy for giving me opportunities to shine, for being patient and supportive of my ideas, and it has been inspiring to see her continued enthusiasm for science. Amy was also the chair of the department during my stay at UConn, and she never lacked time for the group and me. I have asked her many times, “how do you do it?” And her responses have always been inspiring and worth keeping. I became who I am, as a person and a scientist, because of you. I will continue to do my best to become the scientist she wanted me to be, and I will always be grateful for her inspiration.

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discussions on computational studies. Lastly, I want to thank Dr. Chris Senanayake for allowing me to work with his team, for pushing me to do my best, and for his incredible support, not only during my stay at BI but also during the time I was looking for a postdoctoral position.

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The people I met and worked with have tremendously enriched my graduate school experience and for that, I will always be thankful. Former group members who departed before me include Sampada Chitale, Santosh Keshipeddy, Yankee Liang, Song Li, and Kaddy Camara. Sampada was my mentor, and she taught me most of the organic chemistry techniques I know today, and I am happy to have shared them with others I have mentored. I thank her friendship, and I will certainly visit her in Canada someday. I thank Santosh for the numerous discussions and valuable insights, in particular on the Pd-catalyzed amidation of lactones. I also thank him for helping me with chiral HPLC experiments. Song is a great friend, and I am thankful for his help in many ways, inside and outside the lab. Kaddy was my lab buddy for many years. I thank her friendship and encouragement during tough times including those many late nights we spent in the lab.

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My greatest friends and family are my strongest support throughout my graduate school. I want first to thank my *Ateng's* (root word: "*Ate*" – a Tagalog word that means 'elder sister,' slang meaning for *bestie* and family; it comes in different spelling such as *ate*, *ateng*, *'teh*, *'beh* and *antee*). To *ate* Annie, *antee* Joans, Daben *'beh*, *antee* Gill, *ate* Pamz, and *ate* Mia; thank very much. I had more than 90% of my breakfast, lunch, and dinner with them; I go to school and go home with them. I am very much grateful to have them with me during great times and the most difficult moments. I can't imagine what grad school would have been without them. I am also

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Within five difficult years of graduate school, you are one of the very few lucky ones if you met your other half, your partner, or your best friend. I am very fortunate to have met my best friend, Don. We came to UConn in the same year, and both ended up joining the Howell group. We took classes together; struggled on similar exams; we collaborated in the lab, fought on many scientific ideas; and we lived together during our stay at Boehringer Ingelheim. However, it is his invaluable friendship and all the small things we do for each other, that I am most thankful for. Thank you for waiting on me on many occasions, for eating chicken and broccoli whenever I want to eat Chinese food, for eating chicken biryani whenever I want Indian food, for going to BWW with me on most Saturday nights whenever I want to watch UFC, for ~~going~~ not going to my birthday and my *ateng's* birthday parties, for watching movies with us, for the several summer outings, for the fish tank that my *ate's* already claimed as theirs, for ~~eating~~ not eating my mom's specialty, and for ~~waiting~~ not waiting on me when we are both hungry and am still in the middle of an experiment. Thank you for Blinker and I already miss her.

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$^{13}CH_2I_2$	Carbon-13 labeled diodomethane
$[\alpha]^{20}_D$	Specific rotation (at 20 °C)
3-Quinuclidinol	1-Azabicyclo[2.2.2]octan-3-ol
Ar	Aryl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
Bn	Benzyl
br	Broad
c-Hex	Cyclohexyl
c	Concentration; *c* = 1.0 is equivalent to 10 mg sample/mL solution
CA	Conjugate addition
CAL-B (lipase)	*Candida antarctica*; Novozyme 435
Calcd	Calculated
$CDCl_3$	Deuterated chloroform
CD_2Cl_2	Deuterated methylene chloride
$CHCl_3$	Chloroform
CM	Cross-metathesis
cod	1,4-cyclooctadiene
DABCO	1,4-Diazabicyclo[2.2.2]octane
DACH (in Trost ligand)	1,2-Diaminocyclohexane
dba	Dibenzylidene acetone
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarization transfer
dm	Doublet of multiplet
dr	Diastereomeric ratio
ee	Enantiomeric excess
Eq	Molar equivalent
ESI	Electrospray ionization
Et_2O	Diethyl ether
EtOAc	Ethyl acetate

FTIR	Fourier Transform Infrared
HC	Heck coupling
HPLC	High performace liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
J	Coupling constant value
KOH	Potassium hydroxide
m/z	Mass to charge ratio
MBH	Morita-Baylis-Hillman
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Naph	Naphthyl
nbd	Norbornadiene
NMR	Nuclear Magnetic Resonance
Nosyl	Nitrobenzene sulfonyl
OAc	Acetate
$Pd(OAc)_2$	Palladium(II) acetate
Petasis reagent; Cp_2TiMe_2	Bis(η^5-cyclopentadienyl)dimethyltitanium
Ph	Phenyl
PCy_3	Tricyclohexyl phosphine
PPh_3	Triphenyl phosphine
ppm	Parts per million
rt	Room temperature
SEGPHOS	5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
SKP (ligand)	Spiroketal phosphine
TBDPS	*tert*-Butyldiphenyl silyl
THF	Tetrahydrofuran
Tol-D_8	Deuterated toluene
Wilkinson's catalyst, $RhCl(PPh_3)_3$	Tris(triphenylphosphine)rhodium(I) chloride
Zeise's dimer, $[Pt(C_2H_2)Cl_2]_2$	Di-μ-chloro-dichlorobis(ethylene)diplatinum(II)

List of Publications

- **Malapit, C. A.**; Reeves, J. T.; Busacca, C. A. Howell, A. R. Senanayake, C. H.
  Rhodium-Catalyzed Transnitrilation of Aryl Boronic Acids with Dimethylmalononitrile
  Angewandte Chemie International Edition **2016**, *55*, 326–330.
    - Selected as a Hot Paper by Editors

- **Malapit, C. A.**; Howell, A. R.
  Recent Applications of Oxetanes in the Synthesis of Heterocyclic Compounds
  The Journal of Organic Chemistry **2015**, *80*, 8489–8495.

- Reeves, J. T.; **Malapit, C. A.**; Buono, F. G.; Sidhu, K. P.; Marsini, M. A.; Sader, C. A.; Fandrick, K. R.; Busacca, C. A.; Senanayake, C. H.
  Transnitrilation from Dimethylmalononitrile to Aryl Grignard and Lithium Reagents: A Practical Method for Aryl Nitrile Synthesis
  Journal of the American Chemical Society **2015**, *137*, 9481–9488.
    - Selected as "Synfact of the month" of October
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- **Malapit, C. A.**; Chitale, S. M.; Thakur, S. M.; Taboada, R.; Howell, A. R.
  Pt-Catalyzed Rearrangement of Oxaspirohexanes to 3-Methylenetetrahydrofurans: Scope and Mechanism
  The Journal of Organic Chemistry **2015**, *80*, 5196–5209.

- **Malapit, C. A.**; Visco, M. D.; Reeves, J. T.; Busacca, C. A.; Howell, A. R.; Senanayake, C. H.
  Nickel or Cobalt Catalyzed Cross Coupling of Aryl Sulfonic Acid Salts with Grignard Reagents Advanced Synthesis and Catalysis **2015**, *357*, 2199–2204.
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Chapter 1

Platinum Catalyzed Oxetane Expansion via Cyclopropane Activation

Adapted in part from:

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Pt-Catalyzed Rearrangement of Oxaspirohexanes to 3-Methylenetetrahydrofurans: Scope and Mechanism
The Journal of Organic Chemistry **2015**, *80*, 5196–5209

Malapit, C. A.; Howell, A. R.
Recent Applications of Oxetanes in the Synthesis of Heterocyclic Compounds
The Journal of Organic Chemistry **2015**, *80*, 8489–8495

1.1 Introduction

Oxetanes are valuable intermediates in organic synthesis due to their diverse reactivies. Strategies in utilizing oxetanes as synthetic intermediates include: (a) ring opening to afford 1,3-difunctionalized acyclic products, (b) ring expansion to access diverse heterocyclic products, and (c) functionalization at C2 or C3 to obtain novel oxetanes. These transformations are typically achieved using classical methods that often impose challenges in rendering them chemo- and regioselective. Recently, oxetane expansions with high selectivity have been developed by using transition metal catalysis. Successful transformations utilized activating groups such as allyl, aryl, or alkynyl. In this study, we developed a platinum catalyzed oxetane expansion using cyclopropane activation to obtain synthetically valuable 3-methylenetetrahydrofurans.

The following introductory sections will include a background on oxetanes in biologically active compounds and as intermediates in organic synthesis. Recent methods on C2 oxetane functionalization and transition metal catalyzed oxetane expansions are emphasized. Lastly, activation of cyclopropane with platinum to form platinacyclobutanes and their reactivities are described.

1.1.1 Oxetanes in Biologically Active Compounds

Oxetanes are important motifs in synthetic and natural products[1] and have recently received considerable attention as versatile elements in drug discovery.[2] For example, paclitaxel, an FDA approved marketed drug (as Taxol) contains an oxetane ring which was postulated to contribute to the rigidity of the compound.[3] Paclitaxel, together with the structurally related drug docetaxel (marketed as Taxotere), is presently used in cancer chemotherapy.

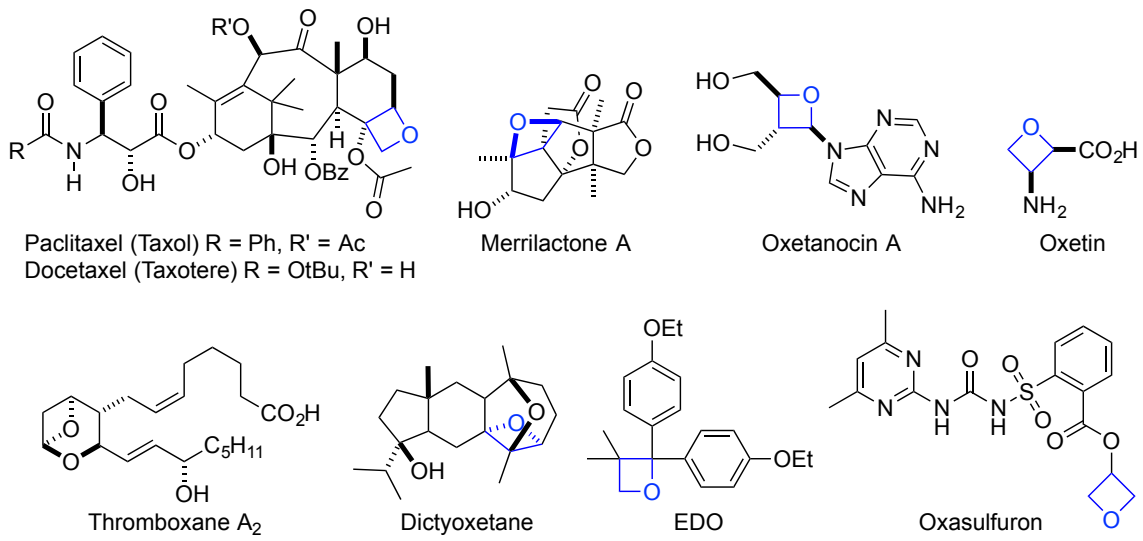


Figure 1. Biologically active natural and synthetic products containing oxetane.

Other natural products that contain an oxetane ring have also shown biologically interesting activities. Oxetanocin A, first isolated from the soil-bacterium *Bacillus megaterium* NK84-0218, inhibits HIV reverse transcriptase by mimicking adenosine. For this reason, commercial and synthetic interest were considerable.[4] Other oxetane containing compounds of biological importance include merrilactone A (rat neuron stimulant),[5] oxetin (herbicidal and antibacterial),[6] thromboxane A_2 (promotes vasoconstriction),[7] dictyoxetane,[8] and others. Anthropogenic small molecules such as EDO[9] and oxasulfuron[10] also incorporate oxetane rings. The insecticide EDO is 25 times more potent than dichlorodiphenyltrichloroethane (DDT). In contrast to DDT, a persistent organic pollutant, EDO is biodegradable.[9]

1.1.2 Oxetanes in Drug Discovery

Oxetanes have remained a neglected unit in medicinal chemistry since the first preparation[11] of the parent structure in 1878. In the past decade, however, a series of reports described the remarkable ability of oxetane units to influence physicochemical properties of drugs and drug candidates. Parameters such as solubility, lipophilicity, hydrogen bond affinity

and metabolic stability of both cyclic and acyclic frameworks were influenced when oxetane was used as a surrogate for other functionalities.[2]

For example, oxetane was viewed as a *gem*-dimethyl equivalent wherein the two methyl groups are bridged by an oxygen atom (Figure 2a).[12] It was reasoned that the polar oxygen in oxetane would compensate for the intrinsic lipophilicity of the *gem*-dimethyl group. Many drugs and drug candidates contain at least one *gem*-dimethyl group, thus highlighting its relevance in drug discovery. Sometimes, the purpose of having *gem*-dimethyl is to block the metabolically unstable benzylic positions in drug candidates.[13] The replacement of benzylic hydrogens with methyl groups, however, can significantly increase the lipophilicity of the molecule. Consequently, the more polar oxetane is viewed as a beneficial surrogate.

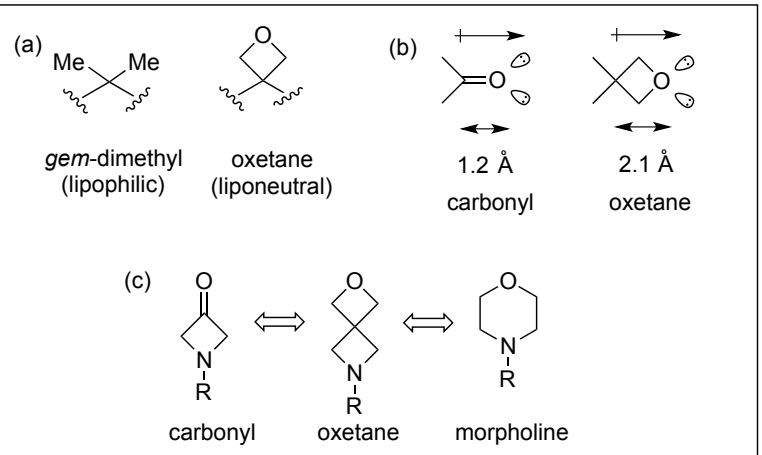


Figure 2. Oxetanes as surrogates for (a) *gem*-dimethyl, (b) carbonyl groups, and (c) morpholines.

It has also been postulated that oxetanes can act as surrogates for carbonyl groups, such as aldehydes and ketones (Figure 2b).[2] The electron lone pairs on the oxygen of oxetane and on the carbonyl groups display comparable spatial arrangements and polarizability. Likewise, the ability of oxetanes to act as hydrogen bond acceptors is almost equivalent to aldehydes and ketones. Replacement of a carbonyl group with an oxetane could be beneficial, since aldehydes and ketones are generally absent in drug discovery because of their inherent chemical and metabolic liability.

Recently, spirocyclic oxetanes were also shown to serve as viable substitutes for morpholine (Figure 2c),[2a] a common moiety in pharmaceutical drugs. Morpholine is often used as a hydrophilic anchor in lipophilic compounds; however, it can also be the target of oxidative clearance mechanisms.

A successful structural modification using oxetanes as modules in drugs was reported in oligonucleotide analogues.[14] Oxetane derivatives of cytidine and thymidine have been examined for their use in antisense oligonucleotides (AONs). The resulting AON-RNA heterodimers displayed increased stability towards degradation by nucleases. Diederich and co-workers showcased the use of oxetanes to enhance the water solubility of a drug candidate.[15] The oxetane appended cytosine showed inhibition of the protein IspE, a potential enzyme target for treatment of malaria.

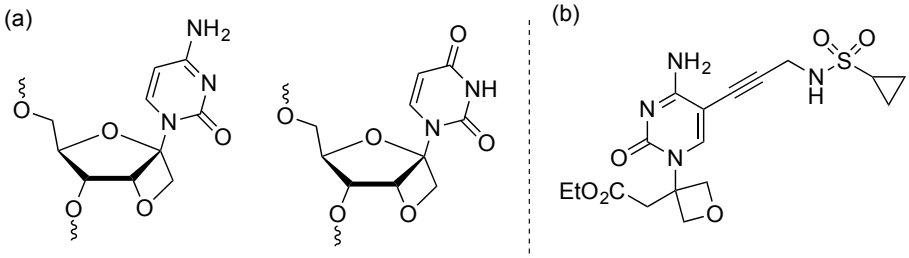
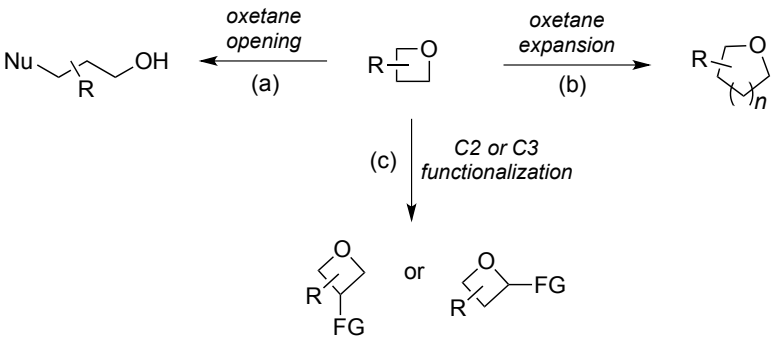


Figure 3. Oxetane-containing analogues of (a) cytidine and thymidine used in novel antisense oligonucleotides and (b) cytosine as inhibitor of IspE.

1.1.3 Reactivities of Oxetanes

The strained nature of oxetanes and the availability of diverse methods for their preparation have provided opportunities for the discovery of novel transformations. In order to take advantage of the reactivities presented in oxetanes, one must consider the following distinct modes of reactivies: (a) ring opening to obtain 1,3-functionalized acyclic products, (b) oxetane-expansion to construct new heterocyclic systems, and (c) functionalization at C2 or C3 to obtain oxetane intact products (Scheme 1). Numerous advances have been made in

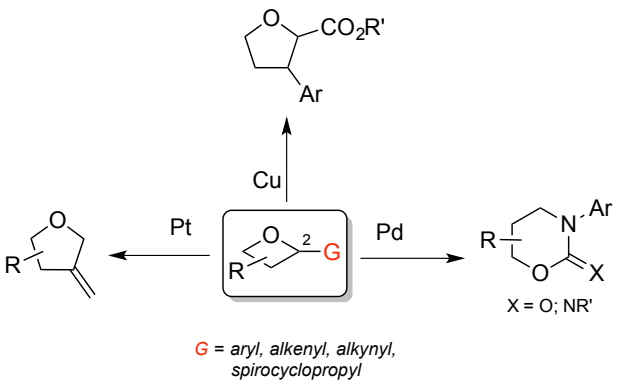
the ring opening[16] of oxetanes to obtain 1,3-functionalized acyclic products or polymers. However, the utility of oxetanes in expansion reactions to contruct new heterocycles is still at its infancy. In this section, strategies to exploit the potential of oxetanes as synthetic intermediates to construct biologically important heterocycles is discussed. Likewise, methods for the functionalization of oxetanes specifically at C2 will be reviewed.



Scheme 1. Reactivities of oxetanes: (a) oxetane opening to form 1,3-functionalized acyclic products, (b) ring-expansion to form new heterocycles and (c) C-2 and C-3 functionalization of oxetanes.

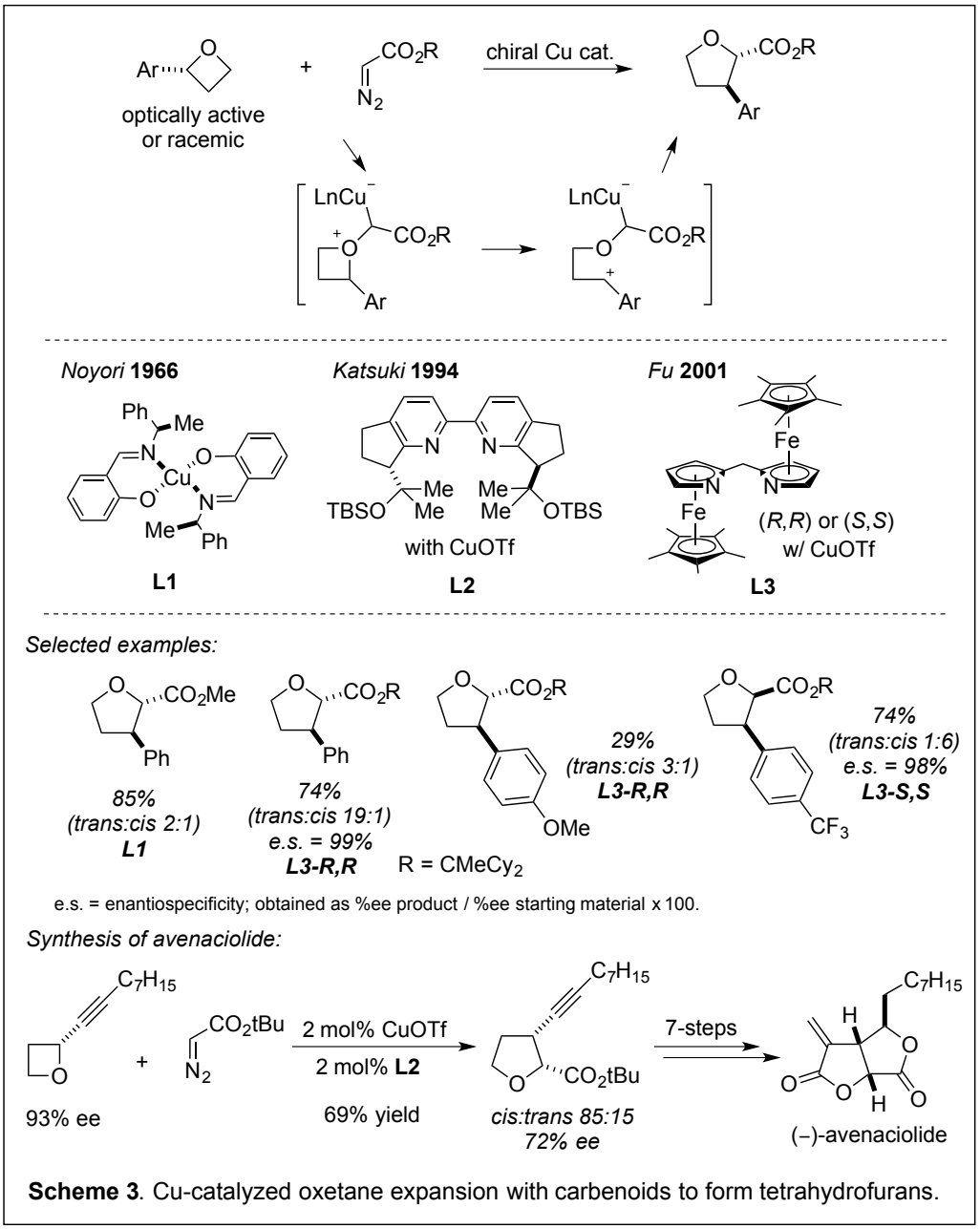
1.1.3.1. Metal catalyzed ring expansions of oxetanes

Most of the recent oxetane ring expansions reported in the literature rely on transition metal catalysis and the presence of an activating group at C2 (Scheme 2). One of the earliest reports of an oxetane expansion reaction dates back to 1966 when Noyori and coworkers demonstrated the asymmetric insertion of methyl diazoacetate into 2-phenyloxetane to form 3-phenyltetrahydrofuranyl-2-carboxylate under chiral Cu(II) catalysis (Scheme 3).[17]



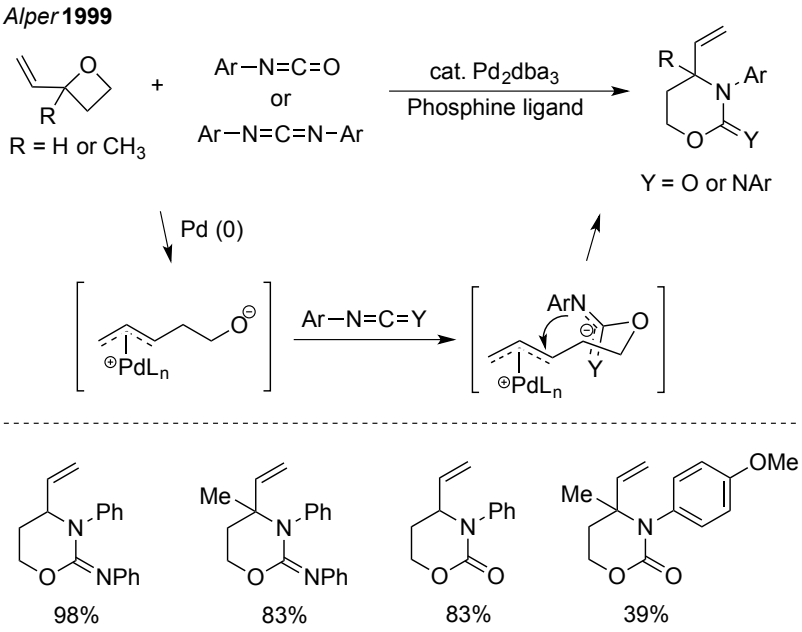
Scheme 2. Selected transition metal catalyzed expansion of C-2 activated oxetanes.

This remarkable copper catalyzed transformation was revisited by Katsuki[18] and Fu,[19] using chiral bipyridine and bisazaferrocene Cu complexes, respectively, to furnish 2,3-disubstituted tetrahydrofurans with moderate to good diastereoselectivities (Scheme 3). Mechanistic studies done by Katsuki suggested that these carbenoid insertions proceed through oxygen ylides (and perhaps zwitterionic intermediates) that undergo ring expansion, with the regioselectivity controlled by the presence of the stabilizing aromatic moiety at C2. Katsuki showcased the utility of the overall insertion in the total syntheses of *trans*-(+)-whisky lactone and (-)-avenaciolide,[18f,18b] where the C2 stabilization came from acetylenic moieties.



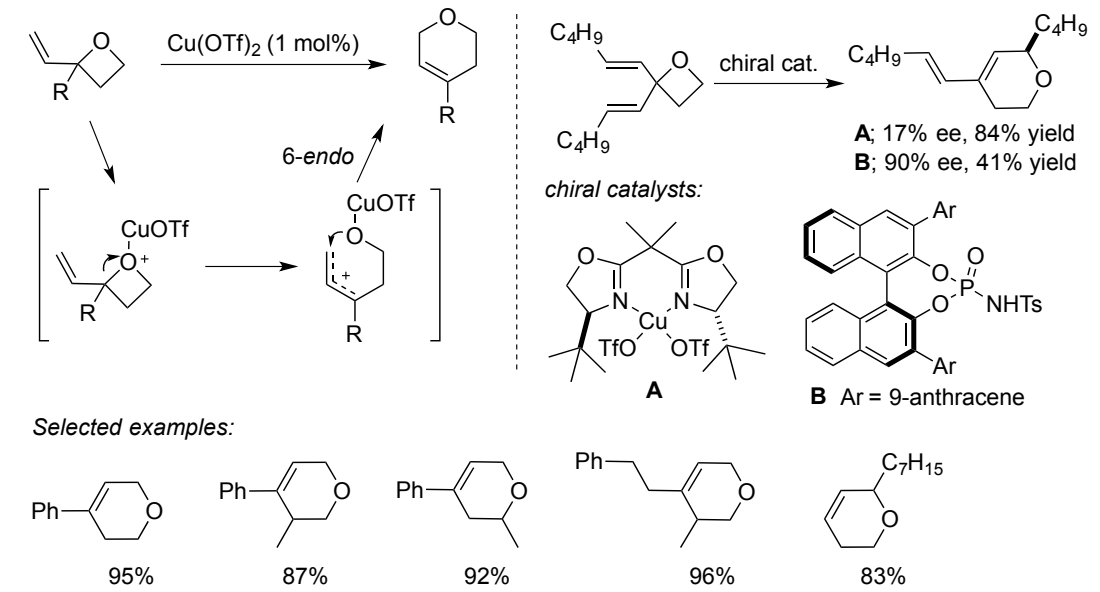
Scheme 3. Cu-catalyzed oxetane expansion with carbenoids to form tetrahydrofurans.

The C2 activation strategy was utilized by Alper and coworkers using a vinyl group as activator.[20] Under Pd catalysis, several vinyl oxetanes reacted with heterocumulenes via a net cycloaddition to form 6-membered heterocyles (Scheme 4). It was proposed that the transformation involves the formation of a Pd-allyl intermediate.



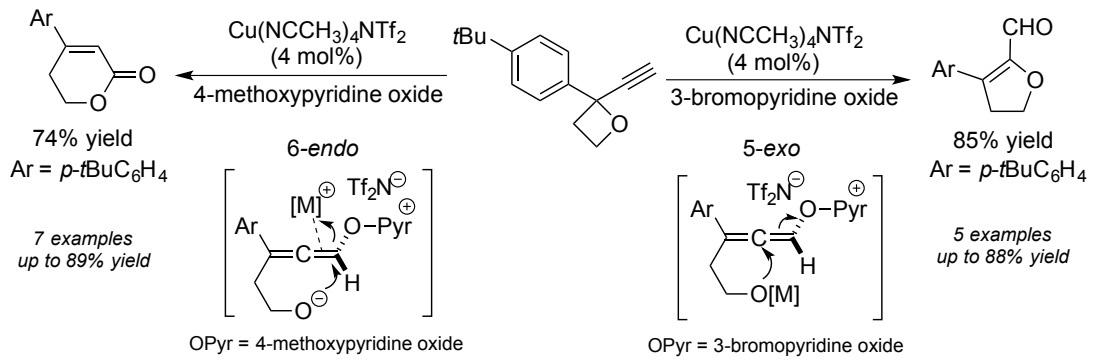
Scheme 4. Pd-catalyzed expansion of vinyl oxetanes with heterocumulenes.

From a successful copper catalyzed ring expansion of vinyl oxiranes, Njardason and and his group have further demonstrated the utility of vinyl oxetanes, showing they can also be opened to allylic intermediates using copper catalysts (Scheme 5).[22] The transformations proceeded with high efficiency under $Cu(OTf)_2$ catalysis. Brønsted acids, such as TfOH and *p*-TsOH, were also found to catalyze this process. The outcome led to the proposal that the reaction proceeds through an allylic intermediate, which undergoes cyclization with the oxygen atom in a 6-*endo* fashion. Furthermore, an enantioselective version was achieved by the desymmetrization of a dialkenyl oxetane using chiral catalysts. Although yields were lower compared to copper catalysis, chiral phosphoric acids/amides provided the dihydropyrans in up to 90% e.e.



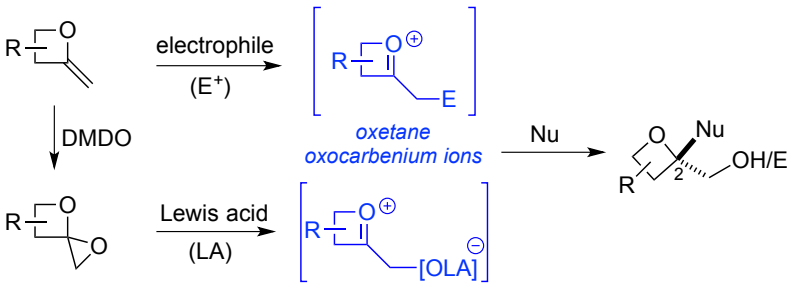
Scheme 5. Cu-catalyzed ring expansion of vinyl oxetanes.

Gagosz and coworkers have cleverly used dual C2 activation (aryl and alkylnyl) to promote oxidative Cu(I)-catalyzed ring expansion of oxetanes (Scheme 6).[23] An interesting divergence in product selectivity was delivered by varying the nature of the pyridine oxide oxidant. Mechanistically, it was proposed that the formation of lactone or dihydrofuranaldehyde could originate from the same allenyloxypyridinium intermediate. It was found that the electron-deficient oxidant, 3-bromopyridine oxide, gave exclusive formation of dihydrofuranaldehyde, since 3-bromopyridine is a good leaving group during the 5-*exo* cyclization. In contrast, use of the more electron-rich oxidant, 4-methoxypyridine oxide, favored cyclization in a 6-*endo* fashion, providing only 6-membered lactones.



Scheme 6. Cu-catalyzed ring expansion of alkynyl and aryl oxetanes.

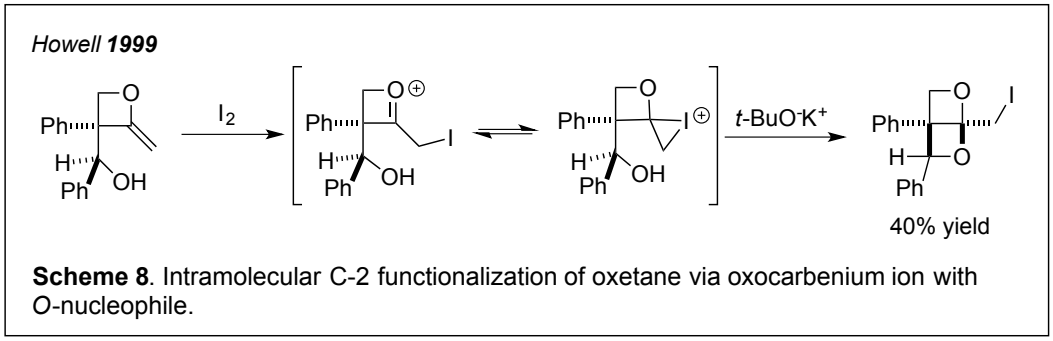
1.1.3.2 C-2 Functionalization of oxetanes via oxocarbenium ion



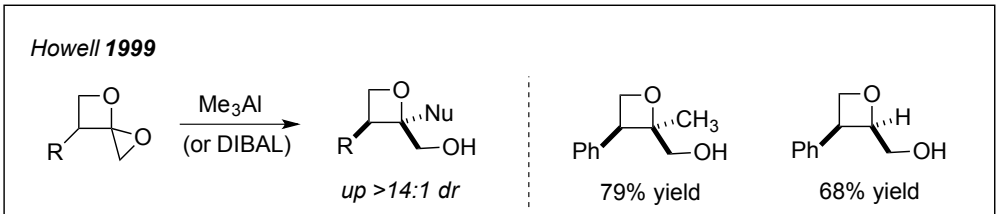
Scheme 7. Oxetane oxocarbenium ion from 2-methyleneoxetane or dioxaspirohexane and reaction with nucleophiles to obtain C-2 functionalized oxetanes.

In the last two decades, the Howell group has engaged in the development of methods for the preparation and exploitation of oxetanes. In particular, we reported the first general approaches to 2-methyleneoxetanes[24] and 1,5-dioxaspiro[3.2]hexanes.[25] In exploring the reactivities of these unusual oxetanes, we found an analogous reactivity in the generation of oxetane oxocarbenium ions when treated with suitable Lewis acids or electrophiles (Scheme 7). These oxocarbenium ions were intercepted with nucleophiles, and the reaction outcome has been diverted to two distinct pathways, ring opening or 1,2-addition.[24-32] While there have been several functionalization strategies for oxetanes,[2,33] specifically at the C-3 position, in this section our work on the generation of oxetane oxocarbenium ions and their reactivity with

nucleophiles via 1,2-addition will be discussed. This constitutes an attractive method for functionalization of oxetanes at C-2.



Scheme 8. Intramolecular C-2 functionalization of oxetane via oxocarbenium ion with *O*-nucleophile.



Scheme 9. Intramolecular C-2 functionalization of oxetane via oxocarbenium ion with *C* and *H*-nucleophiles.

Our first report in the generation of an oxetane oxocarbenium was in an intramolecular iodoetherification of a 2-methyleneoxetane to provide the first synthesis of a [2.2.0]-fused ketal system (Scheme 8).[28] In the same year, the generation of oxetane oxocarbenium ions from dioxaspirohexanes was assumed from the outcomes of reactions with DIBAL-H or Me_3Al.[25] In these reactions, aluminum served as a Lewis acid, generating the oxocarbenium ion; subsequent reaction with hydride or a methyl group provided 2-hydroxymethyloxetanes (Scheme 9). We recognized that this protocol offered a way to functionalize oxetanes at the C-2 position, and the methodology was expanded to heteroatom nucleophiles, for example, azide and *N*-heteroaromatic bases.[29,30] The functionalization of oxetanes at C-2 with *N*-heteroaromatic bases appeared to be correlated with the pK_a of the nucleophile, with more acidic nucleophiles (pK_a <10) favoring 1,2-addition while more basic nucleophiles provided mainly ring-opened products (Table 1).

Howell ***2003***

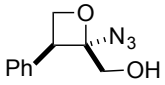
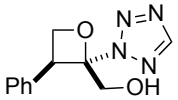
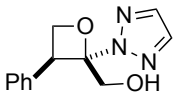
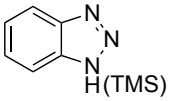
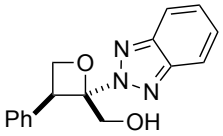
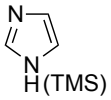
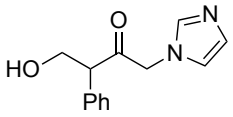
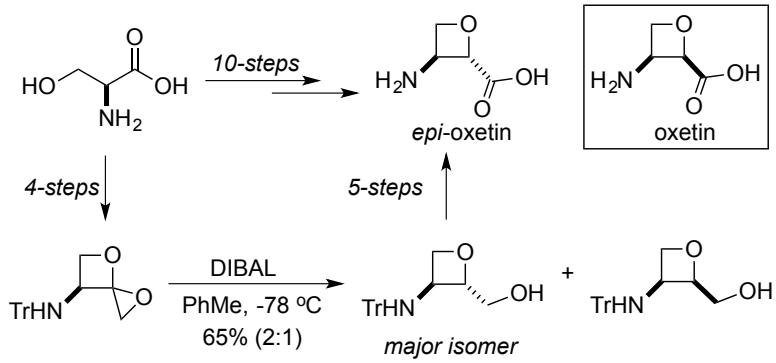
N-nucleophile	pK_a	Products	% Yield
$TMSN_3$	-		68%
	4.9		42%
	9.3		59%
	8.2		45% (40%)
	14.5		50% (28%)

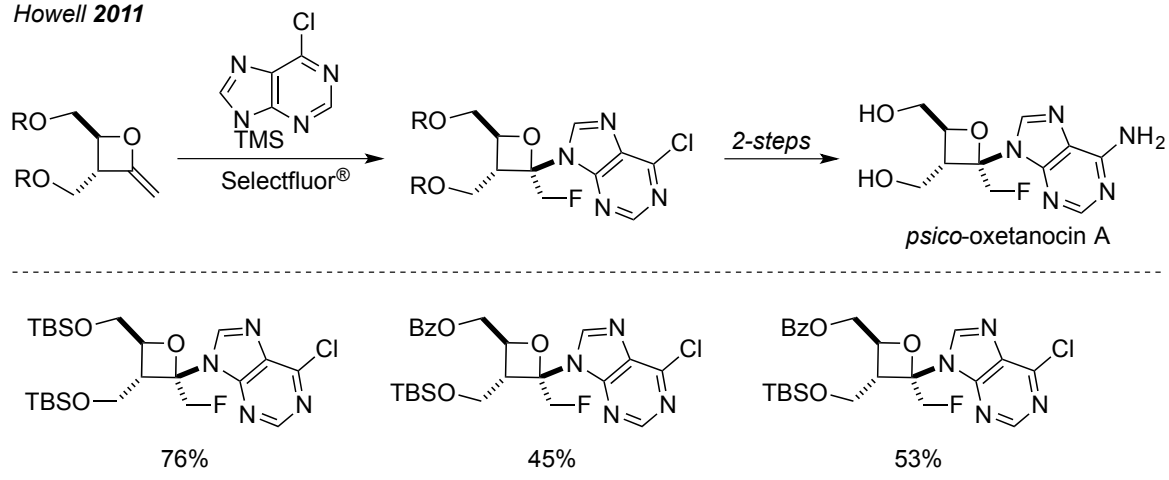
Table 1. Intramolecular C-2 functionalization of oxetane via oxocarbenium ion with *N*-nucleophiles.

The ability to generate and capture oxetane oxocarbenium ions from 2-methyleneoxetanes and dioxaspirohexanes has been exploited in the syntheses of C-2 functionalized oxetanes of biological importance. *epi*-Oxetin was synthesized from an *L*-serine derived dioxaspirohexane, which underwent an aluminum-assisted 1,2-addition with hydride to furnish a 2-hydroxymethyloxetane as the key intermediate (Scheme 10).[31]



Scheme 10. Utility of oxetane oxocarbenium ion in the synthesis of *epi*-oxetin.

Recently, the group developed a F^+-mediated C-2 incorporation of nucleobases to 2-methyleneoxetanes to access oxetanocin-type frameworks (Scheme 11).[32] This method was used in the synthesis of the first *psico*-oxetanocin analog of the powerful antiviral natural product, oxetanocin A (see Figure 1).



Scheme 11. Utility of oxetane oxocarbenium ion in the synthesis of *psico*-oxetanocins.

1.1.4 The Chemistry of Platinacyclobutanes

1.1.4.1. Formation of stable platinacyclobutanes

Activation of C−C bonds in the presence of transition metal complexes is a challenge in organic and organometallic chemistry. However, activation of C−C bonds in cyclopropanes with transition metals (e. g. Pt, Rh, Ni) to form metallacyclobutanes has been more frequently reported due to the release of ring strain associated with 3-membered rings. The first metallacyclobutane report dates back to 1955 when cyclopropane was reacted with hexaplatinic acid (H_2PtCl_6) to obtain an unknown Pt complex **I**.[34] Treatment of complex **I** with pyridine gave a Pt complex with a proposed structure having cyclopropanes coordinated to Pt via an edge complexation mode (Figure 4a). The structure of the initial Pt complex **I** obtained by Tipper was identified independently by Chatt[35] and Gilliard[36] as a tetrameric complex involving platinacyclobutanes (Figure 4b).

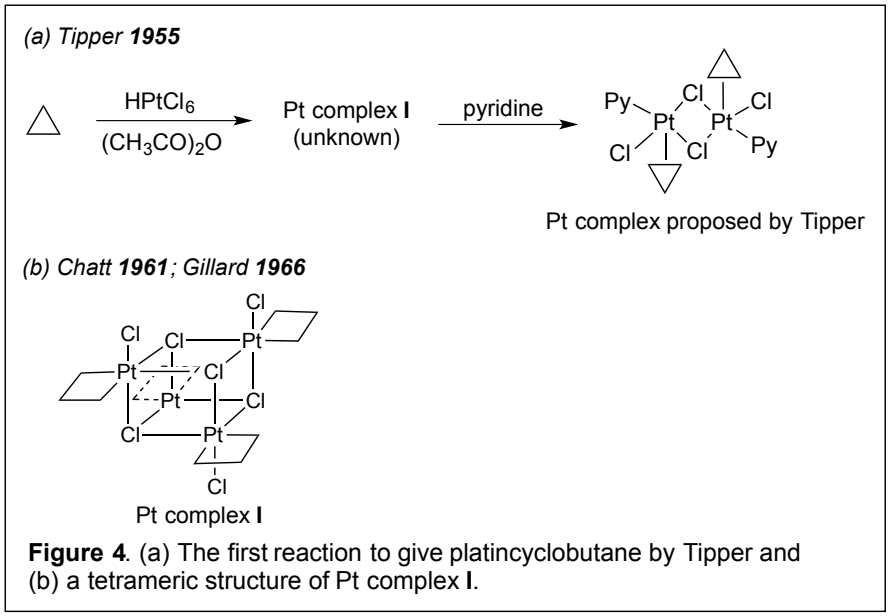
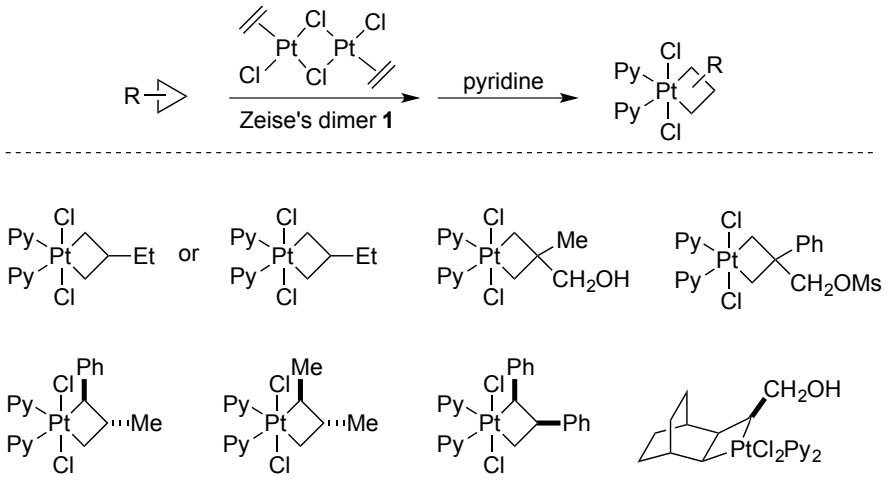
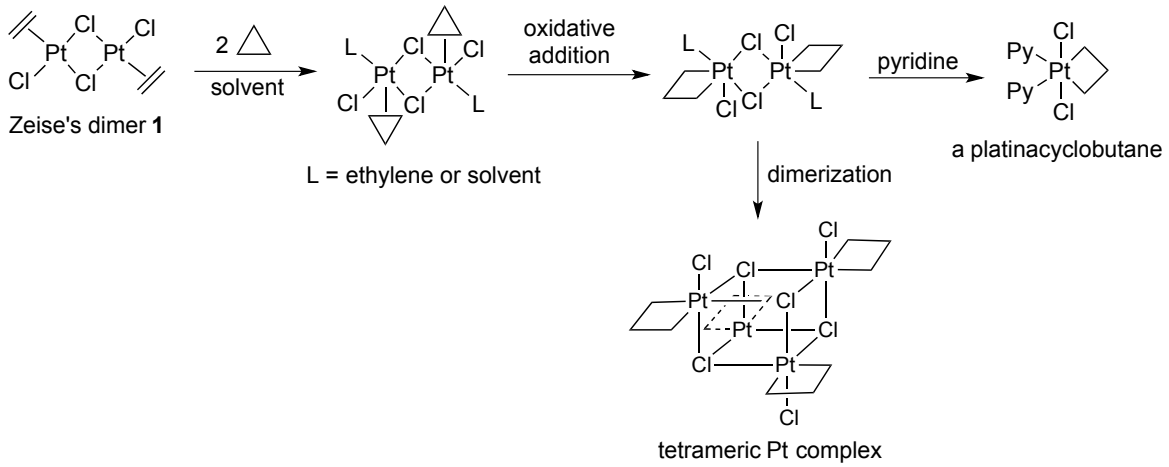


Figure 4. (a) The first reaction to give platincyclobutane by Tipper and (b) a tetrameric structure of Pt complex **I**.



Scheme 12. Examples of platinacyclobutanes generated from cyclopropanes and Pt(II) complex, Zeise's dimer **1**.

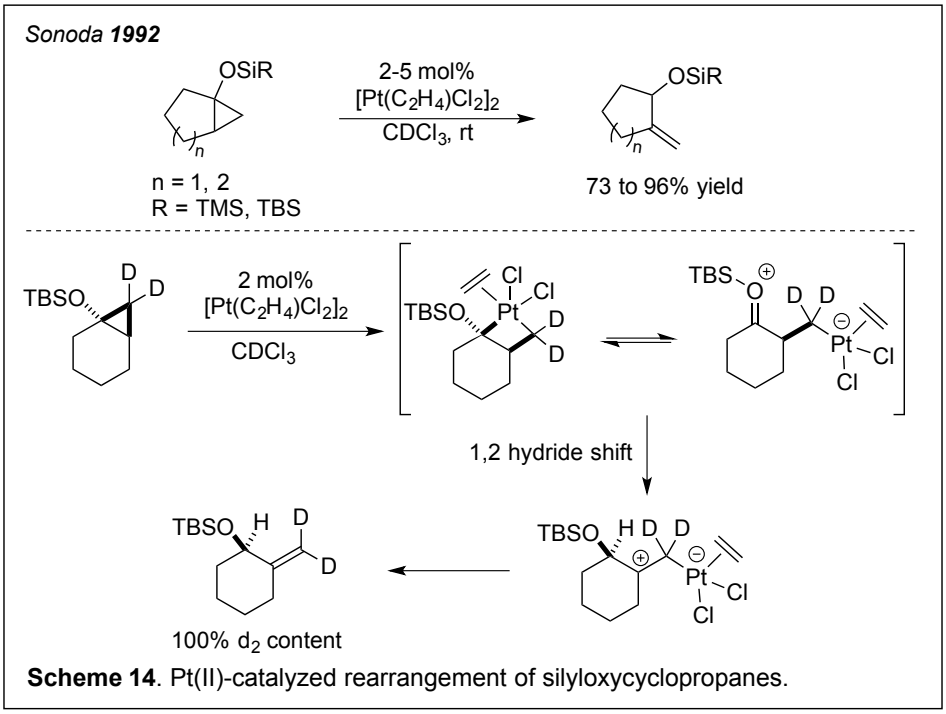
Several stable platinacyclobutanes were obtained using Ziese's dimer $[Pt(C_2H_4)Cl_2]_2$, a more general Pt source (Scheme 12).[37,38] It was believed that the formation of platinacyclobutanes occured by an initial edge-attack of cyclopropane to Pt(II). Subsequently, oxidative addition delivered Pt(IV) platinacyclobutanes. In the presence of a ligand such as pyridine, stable Pt(IV) platinacyclobutanes were obtained and characterized by NMR. In the absence of pyridine, dimerization of the initial platinacyclobutane complex led to a tetrameric Pt(IV) complex (Scheme 13). In the case of 1-substituted and 1,1-disubstituted cyclopropanes, the oxidative addition happened at the least sterically hindered C–C bond (Scheme 12).



Scheme 13. Proposed mechanism for the formation of platinacyclobutane complexes.

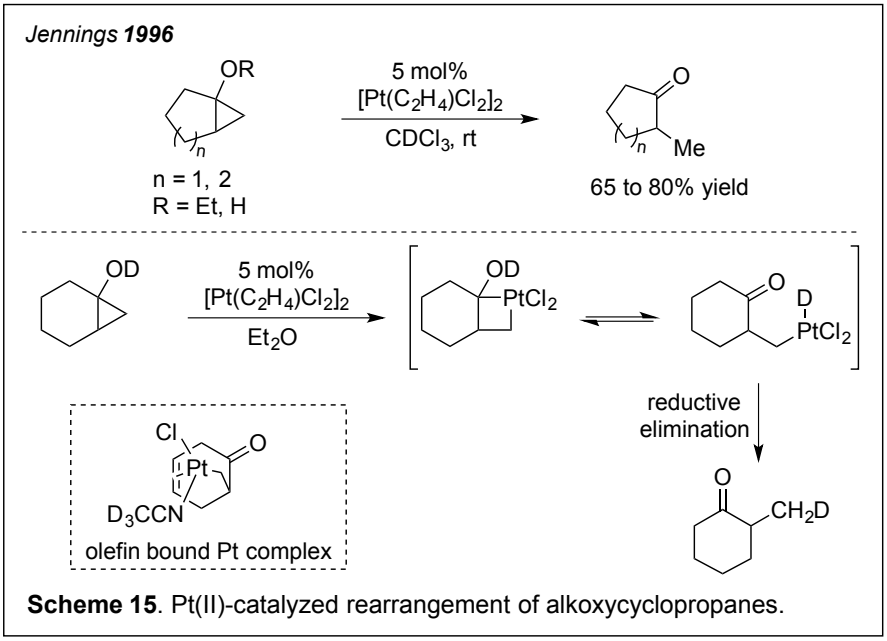
1.1.4.2. Reactions involving platinacyclobutanes

The facile formation of platinacyclobutanes from cyclopropanes and Pt(II) constitutes an interesting C-C bond activation approach. However, due to the observed stability of the platinacyclobutanes obtained, their synthetic utility as intermediates or in a catalytic transformation was limited.[39-42] Sonoda[39] and co-workers first reported a Ziese's dimer catalyzed C-C bond activation for the isomerization of silyloxycyclopropanes to form allyl silyl ethers (Scheme 14). The reaction was found to be completely regio- and stereoselective. Mechanistic studies suggested that β-hydride abstraction provided the olefin. This was confirmed by reacting deuterated silyloxycyclopropane with Ziese's dimer which gave allyl silyl ether product with 100% deuterium content at the methylene carbon. A mechanism that was proposed involves initial formation of platinacyclobutane where Pt undergoes oxidative addition to the C–C bond next to oxygen. This then undergoes ring-opening to form a zwitterionic oxocarbenium ion. β-Hydride migration, followed by reductive elimination, provides the olefinic product.



Scheme 14. Pt(II)-catalyzed rearrangement of silyloxycyclopropanes.

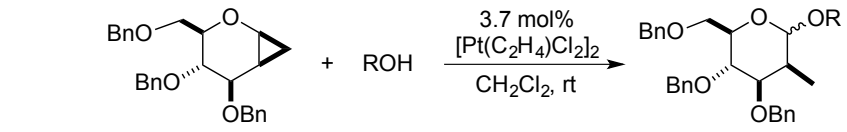
Jennings and Hoberg[40] reported a Zeise's dimer catalyzed isomerization of alkoxycyclopropanes to ketones (Scheme 15). This reaction was also found effective when hydroxycyclopropanes were used. To gain insight into the mechanism, a deuterated cyclopropane alcohol was treated with Ziese's dimer in dry diethyl ether; this gave ketone product with deuteration at the methyl substituent. This led them to propose a mechanism that involves initial formation of a platinacyclobutane intermediate, followed by ring opening and subsequent reductive elimination. In a stoichiometric olefin trapping experiment, a ketone having a Pt-bound to olefin was isolated and characterized by X-ray crystallography.



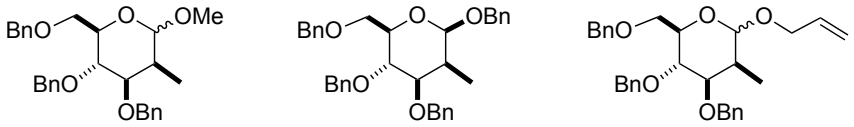
Scheme 15. Pt(II)-catalyzed rearrangement of alkoxycyclopropanes.

Madsen[41] and coworkers reported a ring opening reaction involving 1,2-cyclopropanated sugars with alcohols in the presence of catalytic Zeise's dimer (Scheme 16). This reaction provided C-3 methylated sugars with high selectivity for the α-anomer. When this ring-opening reaction was conducted with deuterated alcohol as the nucleophile, product was obtained having deuteration on the methyl group at C-3. Based on previous mechanistic reports by Jennings, Madsen and coworkers proposed a mechanism that involves initial formation of a platinacyclobutane or platinated oxocarbenium ion intermediate. Subsequent nucleophilic attack by an alcohol, followed by reductive elimination would provide the observed C-2 methylated sugar.

*Madsen **1998***

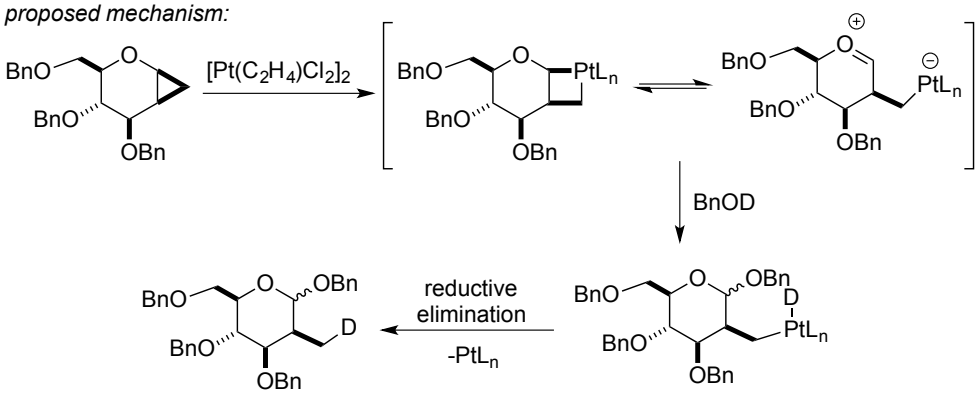


selected examples:



82%; α/β 21:1 95%; α/β 12:1 92%; α only

proposed mechanism:

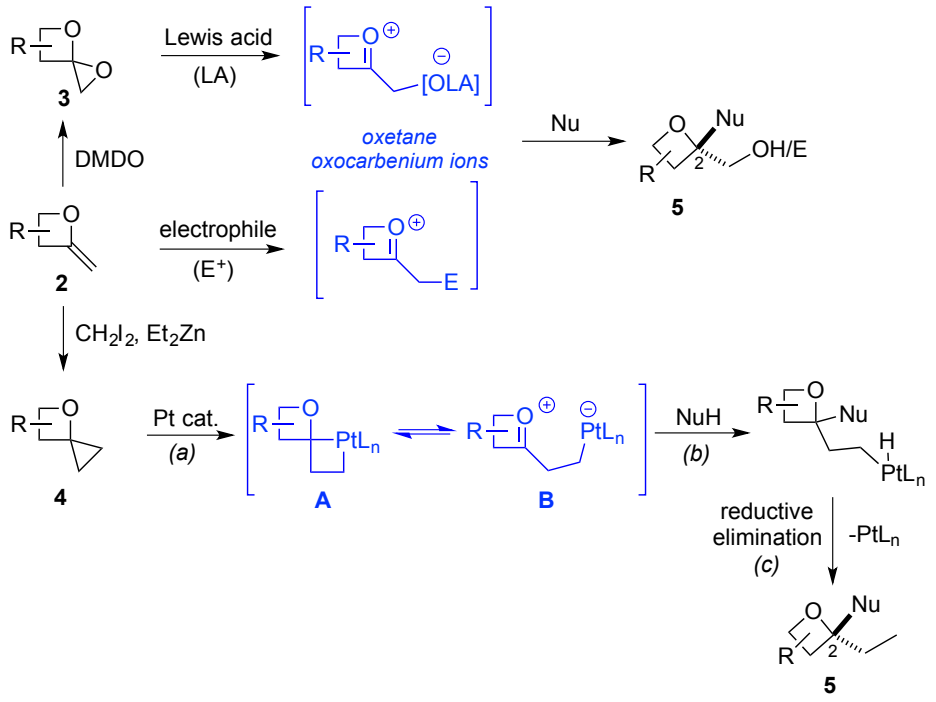


Scheme 16. Pt(II)-catalyzed ring opening of cyclopropanated sugars with *O*-nucleophiles.

1.2 Research Design and Mechanistic Hypothesis

Our success on the C-2 functionalization of oxetanes via the generation of oxetane oxocarbenium ions from methyleneoxetanes **2** or dioxaspirohexanes **3** led us to explore other, starting materials (Scheme 17). We have previously shown that spirocyclopropyloxetanes **4** can easily be generated from Simmon-Smith cyclopropanation of 2-methyleneoxetanes.[43] We envisioned that stable spirocyclopropyloxetanes could generate oxetane oxocarbenium ions similar to those derived from methyleneoxetanes **2** and dioxaspirohexanes **3**.

1.2.1 Mechanistic Hypothesis



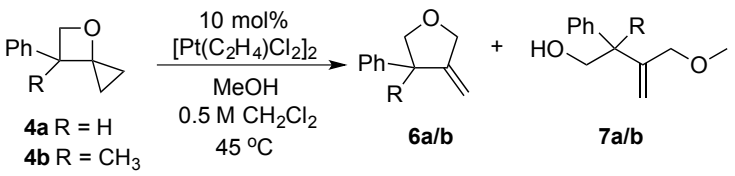
Scheme 17. Mechanistic hypothesis for the Pt(II)-catalyzed ring opening of spiro-cyclopropyloxetanes **4** with nucleophiles to obtain C-2 functionalized oxetanes. Mechanism involves: (a) oxidative addition of Pt(II) to the C–C bond of cyclopropane adjacent to oxygen to form platinacyclobtaune A or oxetane oxocarbenium ion **B**, (b) nucleophilic 1,2 addition, followed by (c) reductive elimination.

Based on previous reports by Madsen[41] on the Pt(II)-catalyzed ring opening of cyclopropanated sugars with alcohols, we postulated that 2,2-disubstituted oxetanes **5** could be accessed as shown in Scheme 17. First, the cyclopropane in spirocyclopropyloxetane **4**

could undergo oxidative addition to Pt(II) to form platinacyclobutane **A** where the platinum is inserted to the C−C bond adjacent to oxygen. This is analogous to oxetane oxocarbenium ion **B**. Second, nucleophilic attack of an external nucleophile would add to the oxocarbenium, leading to the formation of an oxetane-containing Pt complex. Finally, reductive elimination would provide novel C-2 functionalized oxetane with subsequent regeneration of Pt(II) catalyst.

1.2.2 Initial studies

At the onset of this study, spirocyclopyloxetane **4a** (or **4b**) was used as a substrate model and reacted with Zeise's dimer under the Madsen conditions.[41] In the presence of methanol as nucleophile, mixtures of two products, 3-methylenetetrahydrofuran **6a** (or **6b**) and allyl ether **7a** (or **7b**) (Table 2) were obtained, unexpectedly. When the reaction was conducted in the absence of methanol, **4a** was converted to just 3-methylenetetrahydrofuran **6a**, while allyl ether **7a** was the sole isolable product when the reaction was conducted in the presence of excess methanol. Neither outcome could be rationalized by the initial formation of oxetane oxocarbenium ions (Scheme 17). Thus, these initial results represented a novel pathway for reactions between oxygen-substituted cyclopropanes and Zeise's dimer.



4a R = H
4b R = CH_3

6a/b **7a/b**

Entry (subtrate)	MeOH (eq)	[a]Ratio **6**:**7**	Yield **6**	Yield **7**
1 (**4a**)	2.0	1:1.5	-	-
2 (**4b**)	2.0	1:2	-	-
3 (**4a**)	excess (~20 eq)	**7a** only	0	50%
4 (**4a**)	0	**6a** only	34%	0

Reaction conditions: 0.5 to 1.0 mmol **4a/b**; [a]Ratios are based on ^{1}H NMR of the crude reaction mixture. Yields are isolated yields.

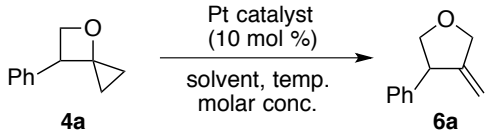
Table 2. Initial findings on the reaction of spirocyclopropyloxetanes with catalytic Zeise' dimer.

3-Methylenetetrahydrofurans are highly sought intermediates in organic chemistry and are also found in several biologically important natural products.[43] With the unanticipated Pt-catalyzed expansion of spirocyclopropyloxetanes to synthetically useful 3-methylene-tetrahydrofurans, we decided to optimize the reaction and explore the scope of this transformation. Likewise, since it was evident that oxidative addition of Pt was not occurring in the cyclopropane adjacent to the C-O bond, we conducted mechanistic studies. ^{13}C-Labeling coupled with ^{13}C-DEPT NMR studies provided clear evidence of an alternative oxidative addition of Pt to cyclopropane. These results are described in the next section.

1.3 Results and Discussion

1.3.1 Optimization of the reaction

Several parameters to optimize the expansion of spirocyclopropyloxetanes to 3-methylenetetrahydrofurans were initially examined by Sampada Chitale and Meena Thakur (Table 3).[44] Evaluation of solvents for the reaction showed that non-coordinating solvents, such as methylene chloride, chloroform, and toluene, gave cleaner conversion of spirocyclopropyloxetane **4a** to 3-methylenetetrahydrofuran **6a** at concentrations from 0.2 to 1.0 M. Solvents such as diethyl ether, tetrahydrofuran and ethyl acetate gave poor reaction outcomes.



4a **6a**

entry	solvent	Pt catalyst	temp	conc (M)	time[a] (h)	% conv.[b] (yield)
1	CD_2Cl_2	**1**	rt	0.2	20	65
2	CD_2Cl_2	**1**	rt	0.5	20	100
3	CD_2Cl_2	**1**	rt	1.0	20	100
4	CD_2Cl_2	**1**	45 °C	0.5	1	100
5	CD_2Cl_2	**1**	45 °C	1.0	1	100 (34%)
6	$CDCl_3$	**1**	55 °C	1.0	0.75	100 (30%)
7	tol-D_8	**1**	80 °C	1.0	0.5	100 (25%)
8	CD_2Cl_2	$PtCl_2$	45 °C	1.0	20	0
9	tol-D_8	$PtCl_2$	80 °C	1.0	20	0
10	CD_2Cl_2	$CODPtCl_2$	45 °C	1.0	20	0
11	CD_2Cl_2	C_2H_2-$Pt(PPh_3)_3$	45 °C	1.0	20	0
12	CD_2Cl_2	$(dfmp)_2PtMe_2$[c]	45 °C	1.0	20	0
13	CD_2Cl_2	$(dfepe)_2PtEt_2$[d]	45 °C	1.0	20	0

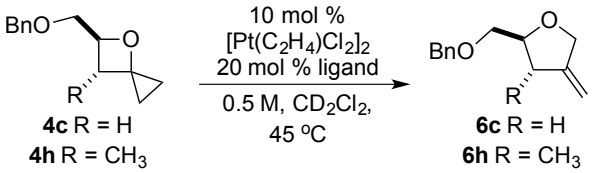
[a]Time to complete consumption of the starting material or until a reaction time of 20 h.
[b]Conversions were monitored by ^1H NMR (isolated yields in parentheses).
[c]Dfmp; $Me(C_2F_5)_2P$.
[d]Dfepe; $(C_2F_5)_2PCH_2CH_2P(C_2F5)_2$.

Table 3. Optimization of conditions for the Pt-catalyzed expansion of spirocyclopropyloxetanes to 3-methylenetetrahydrofurans.

When the reaction temperature was increased from room temperature to 45 ^{o}C, the reaction time needed for complete conversion decreased (entries 4-7). Subsequent reactions were conducted at 45 ^{o}C and with a concentration of 0.5 M in CH_2Cl_2.

It was initially reasoned that the rearrangement was initiated by oxidative addition of Pt(II) into the cyclopropane;[37,38] so a variety of Pt catalysts was examined (Table 3, entries 8-13). Oxetane **4a** did not react with the common Pt catalysts shown. This is consistent with literature precedent showing that the formation of platinacyclobutanes is achieved almost exclusively using Zeise's dimer as the Pt source.[37]

Electron-donating ligands have been previously reported to stabilize platinacycle complexes;[37] so several nitrogen and phosphorus ligands were explored. In general, addition of phosphine ligands provided improved reactivity and increased isolated yields (Table 4). However, no reaction was observed when an electron withdrawing phosphine ligand was used (entry 3), even after 20 h of heating. In contrast, tricyclohexylphosphine and triethylphosphite decreased reaction times to 1 h or less and provided increased isolated yields (up to 70%). The reaction could also be performed at room temperature with no diminution in yield (entries 10, 12 and 13). When this reaction was performed with decreased catalyst loading (5 instead of 10 mol%) at room temperature, clean conversion was still attainable giving 73% yield of product (entry 13). Although triethylphosphite provided the highest yield for **4h**, tricyclohexylphosphine gave better results for a broader range of substrates.



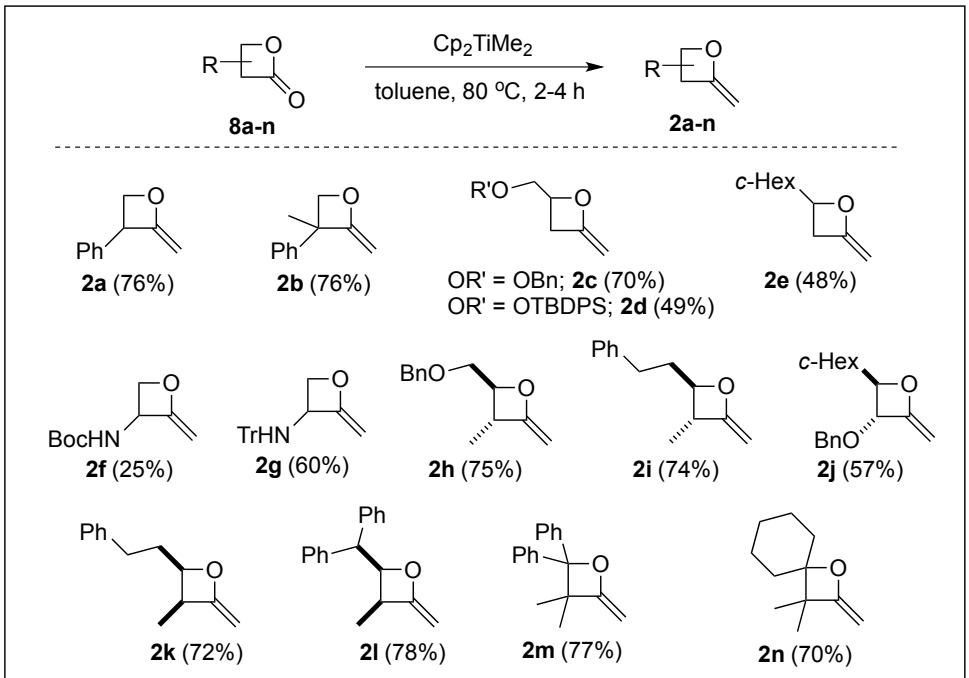
entry	substrate	ligand (mol %)	time[a]	isolated yield
1	**4h**	none	2.5 h	41%
2	**4c**	PPh_3 (20)	20 h	34%
3[b]	**4c**	$P(C_6F_5)_3$ (20)	20 h	0%
4	**4h**	P(*t*-Bu)$_3$ (20)	2 h	60%
5	**4h**	P(*n*-octyl)$_3$ (20)	4.5 h	66%
6	**4h**	bipyridine (10)	2.25 h	61%
7	**4h**	DCPE (10)	30 min	70%
8	**4c**	PCy_3 (20)	45 min	64%
9	**4h**	PCy_3 (20)	40 min	69%
10[c]	**4h**	PCy_3 (20)	6 h	70%
11	**4h**	$P(OEt)_3$ (20)	15 min	68%
12[c]	**4h**	$P(OEt)_3$ (20)	4 h	72%
13[c,d]	**4h**	$P(OEt)_3$ (10)	6 h	73%

[a]Reaction time based on complete consumption of starting material as monitored by ^{1}H NMR; [b]After 20 h no conversion was observed; [c]Reaction run at room temperature; [d]Catalyst loading decreased to 5 mol %.

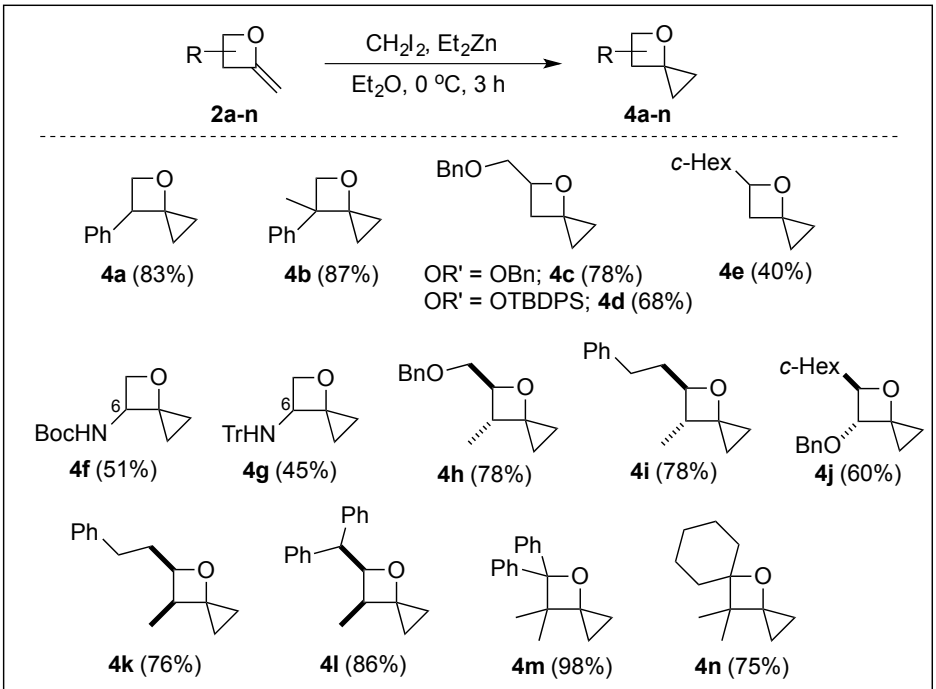
Table 4. Survey of ligands for the Pt-catalyzed expansion of spirocyclopropyl-oxetanes to 3-methylenetetrahydrofurans.

1.3.2 Preparation of spirocyclopropyloxetane substrates

A variety of spirocyclopropyloxetanes **4a-n** was prepared to explore the scope of the ring expansion. The starting β-lactones were prepared from previously reported lactonization procedures (see Experimental Section for details). Methylenations of various β-lactones were conducted using our previously reported protocol by reacting them with dimethyltitanocene in toluene.[24] The methyleneoxetanes were obtained in good yields (Scheme 18). The spirocyclopropyloxetanes were synthesized from the corresponding 2-methyleneoxetanes **2a-n** in moderate to high yields by a modified Simmon-Smith cyclopropanation (Scheme 19).[43] Spirocyclopropyloxetanes **2b**, **2d**–**2g** and **2m** were previously prepared by Sampada Chitale[44a] and Meena Thakur.[44b]



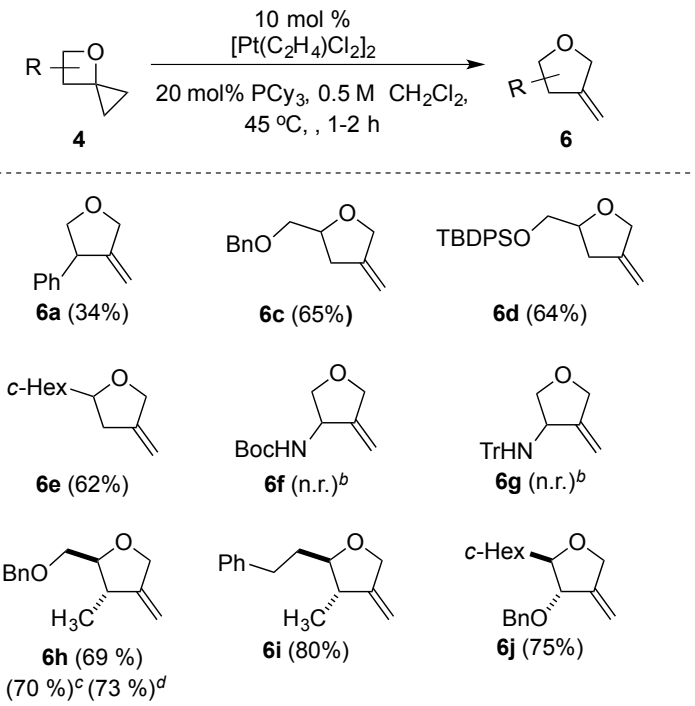
Scheme 18. 2-Methyleneoxetanes prepared from methylenation of β-lactones.



Scheme 19. Spirocyclopropyloxetanes prepared from cyclopropanation of 2-methyleneoxetanes.

1.3.3 Scope of the Reaction

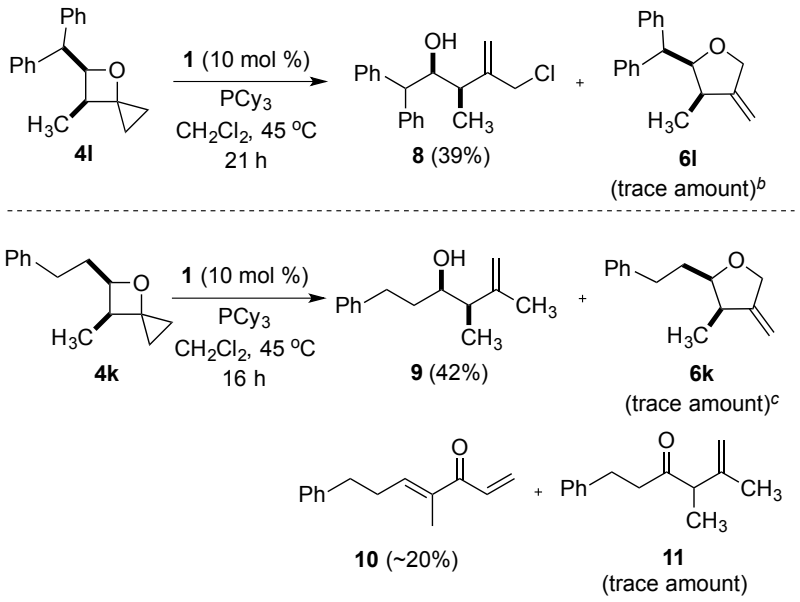
Monosubstituted spirocyclopropyloxetanes rearranged to the corresponding 3-methylenetetrahydrofurans **6c-e** in good yields (Scheme 20). Similarly, *trans*-3-methylenetetrahydrofurans **6h-j** were obtained in up to 80% yield. Also of note, the reaction tolerated most aromatic groups, but for substrates with aryl groups directly attached to the oxetane ring, such as **4a**, poor conversions and low yields were observed. With substrates containing protected amine substituents at C-6 (**4f** and **4g**), no conversion was observed even with prolonged heating (20 h), presumably due to the interaction of the catalyst with the nitrogen groups.



[a]Reaction conditions: 0.5 to 1.0 mmol scale, 10 mol % $[Pt(C_2H_4)Cl_2]_2$, 20 mol % PCy_3, 0.5 M in CH_2Cl_2. [b]No reaction was observed even after 20 h. [c]Reaction was conducted at room temperature. [d]Reaction was conducted using 5 mol % $Pt(C_2H_4)Cl_2]_2$, 10 mol % $P(OEt)_3$ at room temperature.

Scheme 20. Scope of the Pt(II)-catalyzed expansion of spirocyclo-propanes to 3-methylenetetrahydrofurans.

Unexpectedly, when 5,6-*cis*-disubstituted spirocyclopropyloxetane **4l** was reacted under the standard conditions, ring opened allyl chloride **11** was isolated as the major product (Scheme 21). When 5,6-cis-disubstituted spirocyclopropyloxetane **4k** was used, ring opened alcohol **12** was obtained in 42% yield. Analysis of the ^{1}H NMR of the crude reaction mixture and the byproducts isolated from column chromatography showed the formation of additional, inseparable olefinic compounds, which could be the source of the hydrogen needed to form the ring opened, reduced alcohol **12**.



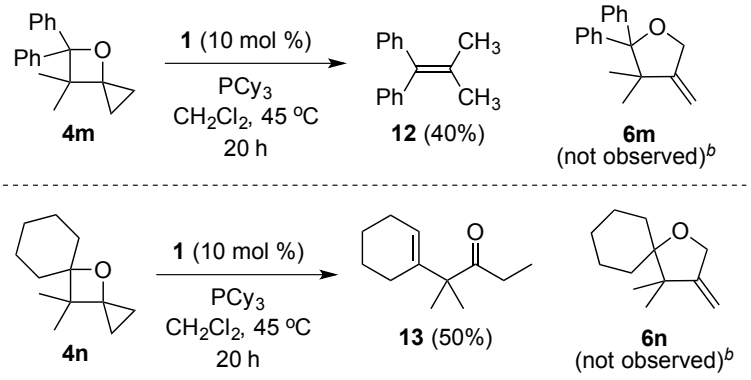
[a]Reaction conditions: 0.5 mmol scale, 10 mol % **1**, 20 mol % PCy_3, 0.5 M in CH_2Cl_2. [b]*Cis*-3-methylenetetrahydrofuran **6l** was isolated in a trace amount and characterized (see Experimental Section). [c]*Cis*-3-methylenetetrahydrofuran **6k** was isolated as a mixture with **11**.

Scheme 21. Reaction of cis-substituted spirocyclopropyloxetanes under Pt(II) catalyst.

It is worth noting that consumption of both 5,6-*cis*-disubstituted spirocyclo-propyloxetanes took longer than was required for the 5,6-*trans*-disubstituted compounds. The formation of the reduced product **12** necessitates a source of a hydride. This could come from tricyclohexylphosphine. When **4k** was treated with Zeise's dimer in the absence of tricyclohexylphosphine, the same products were observed, although the reaction times were

even longer. The rearranged products, 3-methylenetetrahydrofurans **6l** and **6k**, were isolated, but in trace amounts. These alternative outcomes, and the longer reaction times will be discussed later.

Tetrasubstituted-spirocyclopropyloxetanes **4m** and **4n** provided completely different results (Scheme 22). When 5,5-diphenylsubstituted spirocyclopropyloxetane **4m** was treated with Zeise's dimer, no 3-methylenetetrahydrofuran resulted; instead, tetrasubstituted alkene **12** was isolated in 40% yield. On the other hand, 5,5-dialkyldisubstituted spirocyclopropyloxetane **4n** provided α,β-unsaturated ketone **13** in 50% yield as the only isolable product. The different results with **4m** and **4n** and with the spirocyclopropyloxetane with *cis*-substituents on the oxetane ring again led us to question the pathway of these Pt promoted processes.



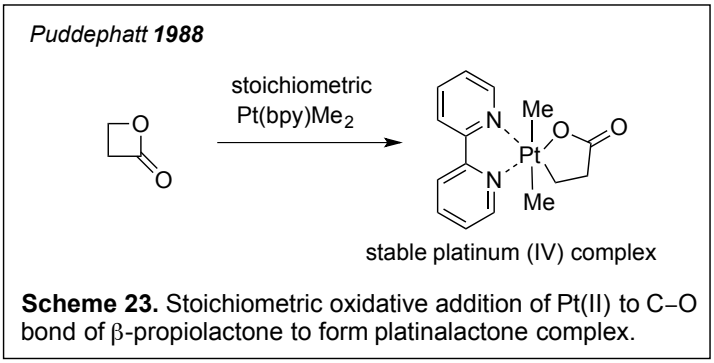
[a]Reaction conditions: 1.0 mmol scale, 10 mol % **3**, 20 mol % PCy_3, 0.5 M in CH_2Cl_2. [b]Based on the ^1H NMR analysis of the crude mixture.

Scheme 22. Reaction of 5,5-disubstituted spirocyclopropaneoxetanes under Pt(II) catalyst.

1.3.4 Mechanistic Studies

Oxidative additions of Pt(II) to cyclopropanes and to the C–O bond of β-lactones have been reported to produce stable platinacyclobutanes[37] and platinalactone (Scheme 23)[45a] complexes, respectively. Moreover, the formation of platinaoxetanes as intermediates has

been postulated in Pt-mediated activation of epoxides.[45b] Platinacyclobutanes are known to be stable and isolable, with many being well characterized, but there have been no reports of alkoxy-substituted platinacyclobutanes being isolated nor observed spectroscopically. This may be due to favorable formation of oxocarbenium ions resulting in isomerizations to ring opened products (see Section 1.1 Schemes 14-16).[39,40]



Scheme 23. Stoichiometric oxidative addition of Pt(II) to C–O bond of β-propiolactone to form platinalactone complex.

Based on literature precedent related to Pt reactions with strained rings, we hypothesized two potential initial oxidative additions of Pt. These include the oxidative addition of Pt(II) into the cyclopropane ring (Figure 5, path *a*) to produce either intermediate **I** or **II** or oxidative addition into the C-O bond of the oxetane ring (path *b*) to give intermediate **III** or **IV**.

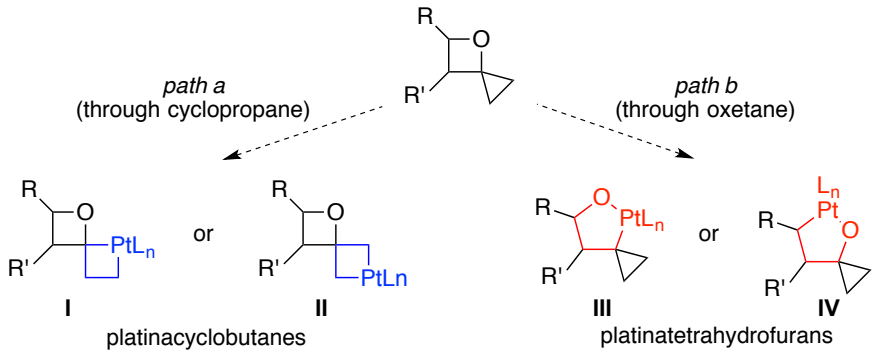
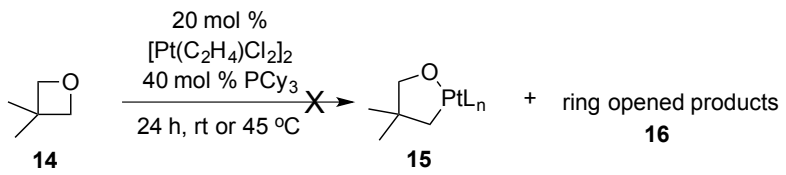


Figure 5. Possible platinacycle intermediates obtained from spirocyclopropyl-oxetanes via the cyclopropane ring (path *a*) or the oxetane ring (path *b*).

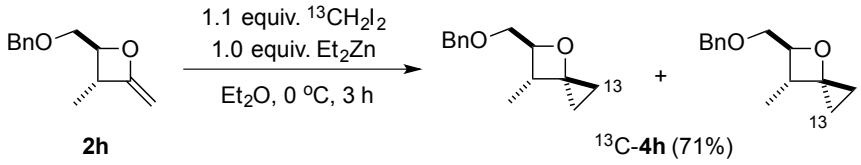
The formation of 3-methylenetetrahydrofurans cannot be rationalized from oxetane oxocarbenium intermediate **I**. Similarly, intermediate **IV** would not lead to the formation of the observed products, and to date, there have been no reports of oxidative addition of Pt(II) into

simple oxetanes. To examine the possible insertion of Pt in simple oxetane rings, 3,3-dimethyloxetane **14** was treated with Zeise's dimer and tricyclohexyl phosphine under our standard conditions, but no reaction was observed, even after prolonged heating and the addition of Pt catalyst up to 20 mol %. However, the outcome with **14** may not represent the potential reactivity of the oxetane moiety in spirocyclopyloxetanes with Pt(II).



Scheme 24. Attempted reaction of simple oxetane with Zeise's dimer to give platinatetrahydrofuran or ring opened products.

In order to determine which path was operational, ^{13}C-labeled spirocyclopropyloxetane ^{13}C-**4h** was synthesized by cyclopropanation of methyleneoxetane **10h** using ^{13}C-labeled diiodomethane (Scheme 25). The labeled compound ^{13}C-**4h** was successfully obtained with a comparable yield of 71% as a pair of isotopic stereoisomers.



Scheme 25. Synthesis of C-13 labeled spirocyclopropyoxetane ^{13}C-**4h**.

^{13}C-labeled **4h** was treated with a stoichiometric quantity of Zeise's dimer and tricyclohexylphosphine in CD_2Cl_2 at room temperature, and the resulting reaction was monitored by ^{13}C NMR. Figure 6 provides a summary of the ^{13}C-DEPT NMR analysis of the reaction as it progressed. Two intermediates with ^{13}C-labeled carbon chemical shifts at 15.04/7.94 ppm (region **A**) and at 49.52/113.70 ppm (regions **B** and **B'**) were observed. These intermediates were present over the course of the reaction (Figure 6b and 6c) and largely disappeared after complete conversion of ^{13}C-**4h** (Figure 6d). Specifically, they were observed

for a span of 3 h when the reaction was monitored at room temperature or could persist for up to 15 h at 0 °C.

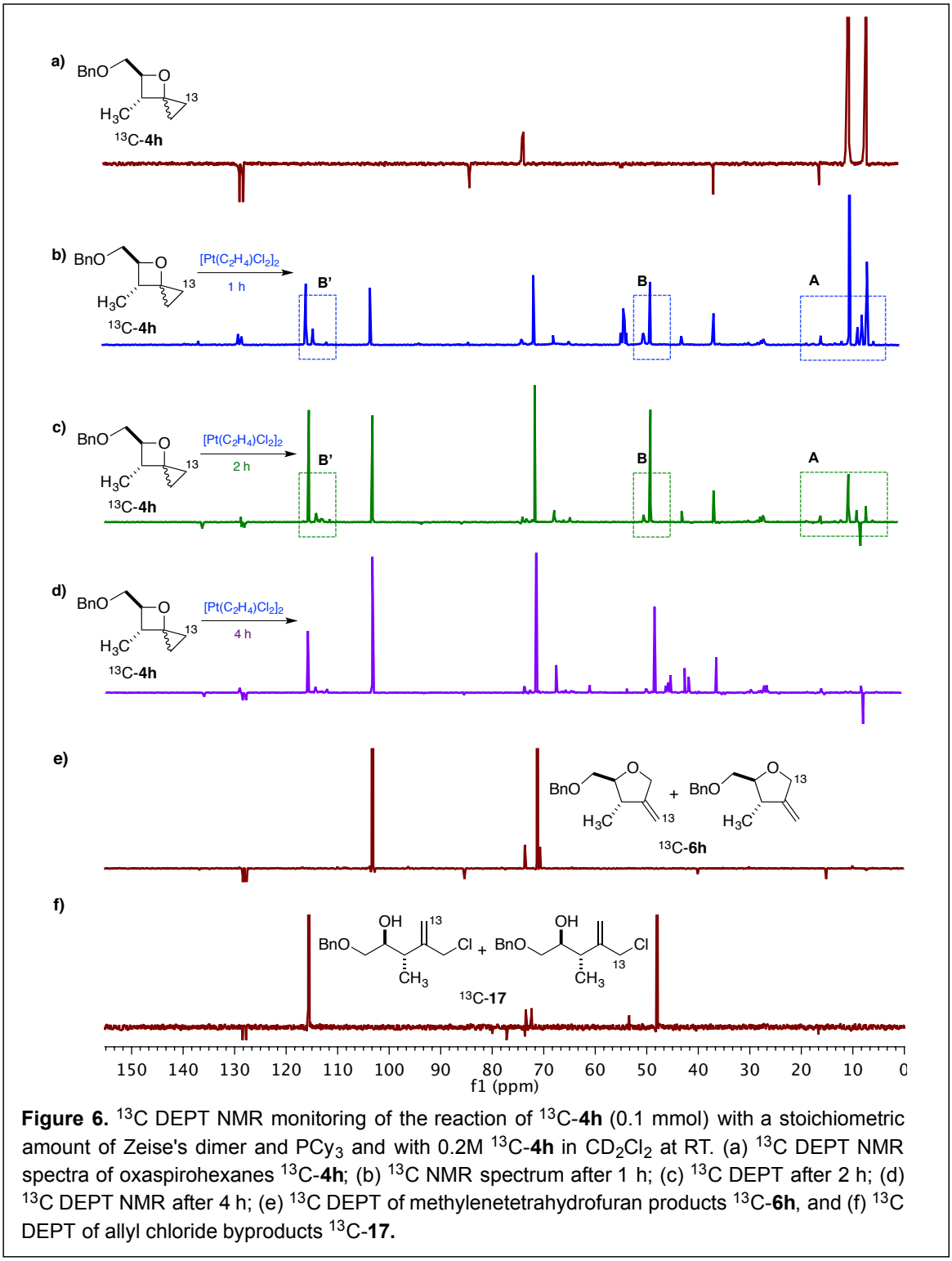


Figure 6. ^{13}C DEPT NMR monitoring of the reaction of ^{13}C-**4h** (0.1 mmol) with a stoichiometric amount of Zeise's dimer and PCy_3 and with 0.2M ^{13}C-**4h** in CD_2Cl_2 at RT. (a) ^{13}C DEPT NMR spectra of oxaspirohexanes ^{13}C-**4h**; (b) ^{13}C NMR spectrum after 1 h; (c) ^{13}C DEPT after 2 h; (d) ^{13}C DEPT NMR after 4 h; (e) ^{13}C DEPT of methylenetetrahydrofuran products ^{13}C-**6h**, and (f) ^{13}C DEPT of allyl chloride byproducts ^{13}C-**17.**

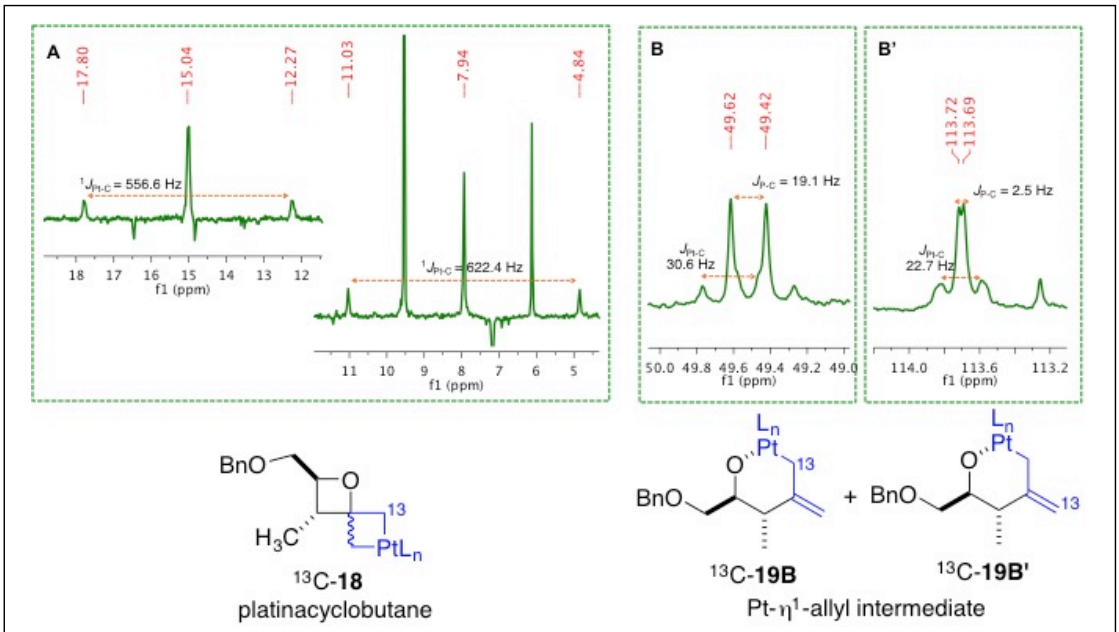


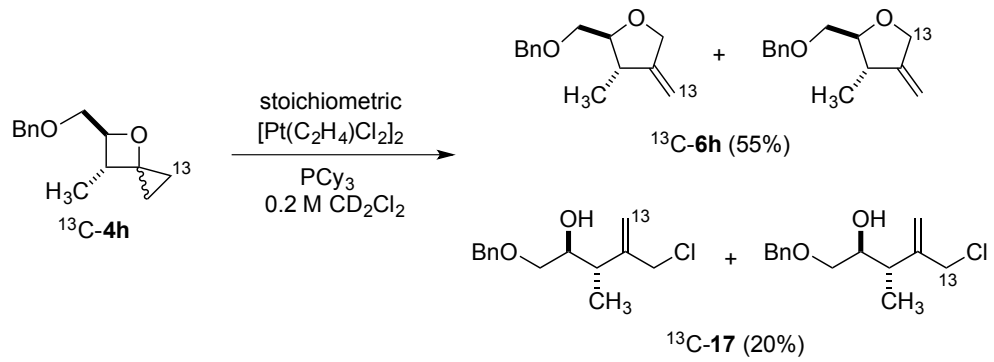
Figure 7. Regions in ^{13}C DEPT NMR monitoring showing the ^{13}C labeled carbon peaks observed as intermediates from the reaction of ^{13}C-**4h** with Zeise's dimer: (A) ^{13}C peaks for platinacyclobutane intermediate ^{13}C-**18** (as a pair of ^{13}C-labeled isotopic stereoisomers), and (B) ^{13}C peaks for Pt-σ-allyl intermediate ^{13}C-**19** as a pair of ^{13}C-labeled isotopic stereoisomers.

The observed ^{13}C-labeled carbon peaks at 15.04 and 7.94 ppm (region **A**) correspond to the expected chemical shifts of carbon sigma bonded to Pt in platinacyclobutanes.[37] These ^{13}C-labeled carbons show large Pt-^{13}C coupling constants of 556.6 and 622.4 Hz, respectively, which fall in the range of usual $^{1}J_{Pt\text{-}^{13}C}$ values in platinacyclobutanes[9] or Pt-C σ-bonds in general.[46] This key intermediate was rationalized to be platinacyclobutane ^{13}C-**18** (as a pair of ^{13}C-labeled isotopic stereoisomers).

The additional ^{13}C-labeled intermediate peaks observed in regions **B** and **B'** were rationalized to be Pt-allyl complexes, which can be obtained from the ring puckering[47] of the oxy-platinacyclobutane ^{13}C-**18**. The large differences in ^{13}C chemical shifts (49.5 and 113.70 ppm) and the $J_{P\text{-}^{13}C}$ values (19.1 and 2.5 Hz, respectively) suggest that the intermediate observed is an η^1 Pt-allyl complex[46,48] as a pair of isotopomers. Specifically, the Pt-η^1-allyl intermediate observed in region **B'** corresponds to ^{13}C-**19B'** as indicated by the small $^{3}J_{Pt\text{-}^{13}C}$

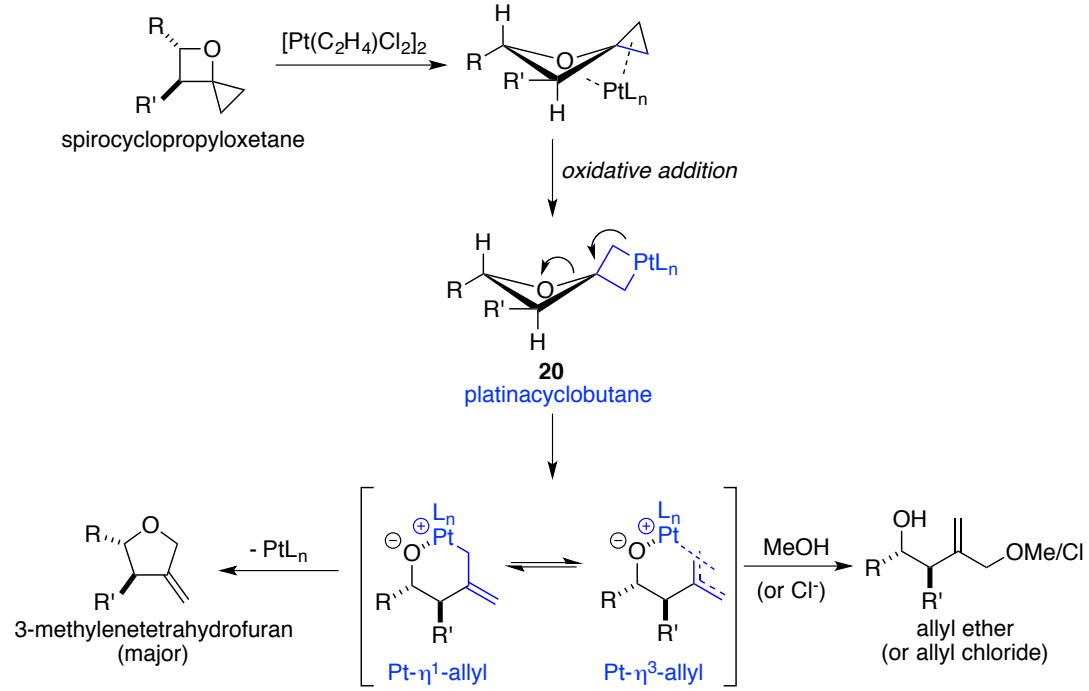
(22.7 Hz), while the intermediate at region **B** corresponds to the other isotopomer, Pt-η^1-allyl ^{13}C-**19B.** Given that the observed $^1J_{Pt\text{-}^{13}C}$ in region **B** (30.6 Hz) is relatively small compared to usual Pt-C σ-bonds[46], the Pt-^{13}C bond must be rather weak.[48] The stability of η^1 and η^3 Pt-allyl complexes is highly dependent on the counterion.[47] It would seem that the Pt allyl intermediate prefers a σ-coordination mode[17] due to the propensity of intramolecular coordination of the negatively charged oxygen atom to the positively charged Pt to form a 6-membered Pt-η^1-allyl complex. Sakaki and co-workers reported that a hydride coordinated Pt-η^1-allyl complex is 8 kcal/mol more stable than its corresponding η^3-allyl complex.[49] Likewise, Pregosin and coworkers have demonstrated that methoxy-modified MOP Pt allyl complexes prefer a σ-coordination mode, albeit with a weak σ-bond.[48] Although the Pt-allyl intermediates observed here appear to be of an η^1 character, the occurrence of Pt-η^3-allyl intermediates is not ruled out. In fact, unresolved peaks were also seen at around 64 and 73 ppm, which may correspond to Pt-η^3-allyl intermediates[46,48] as a pair of isotopomers.

After purification, ^{13}C labeled 3-methylenetetrahydrofurans ^{13}C-**6h** (with ^{13}C peaks at 103.32 and 71.36 ppm, Figure 5e) were isolated in 55% yield as an isotopomeric mixture (Scheme 26). In addition, isotopomeric byproducts, allyl chloride ^{13}C-**17** (with ^{13}C peaks at 115.69 and 48.06 ppm, Figure 6f) were also observed and isolated in 20% yield. The formation of the allyl chloride was not observed when a catalytic amount (5-10 mol%) of Zeise's dimer was used.



Scheme 26. Reaction of ^{13}C-labeled oxaspirohexane ^{13}C-4h with a stoichiometric amount of Zeise's dimer

The evidence delineated above is suggestive of the mechanistic interpretation shown in Scheme 27. First, regioselective oxidative addition of Pt(II) into the least substituted C-C bond in cyclopropane provides platinacyclobutane **20**. Due to the reactivity of oxygen-substituted platinacyclobutanes and perhaps also to the ring strain associated with oxetanes,[50] ring-opening to Pt-allyl complexes results. Cyclization gives 3-methylenetetrahydrofurans **6**. This mechanism is consistent with the formation of allyl ethers/chlorides by intermolecular reactions of the Pt-allyl complexes with methanol or chloride ion when the reaction is conducted in the presence of methanol or a stoichiometric amount of Zeise's dimer. The observed regioselective oxidative addition of Pt(II) into the cyclopropane is remarkable because this has not been the case for all examples of Pt-catalyzed transformations of oxygen-substituted cyclopropanes, where C-C bond cleavage has always occurred adjacent to the oxygen.[39-41]

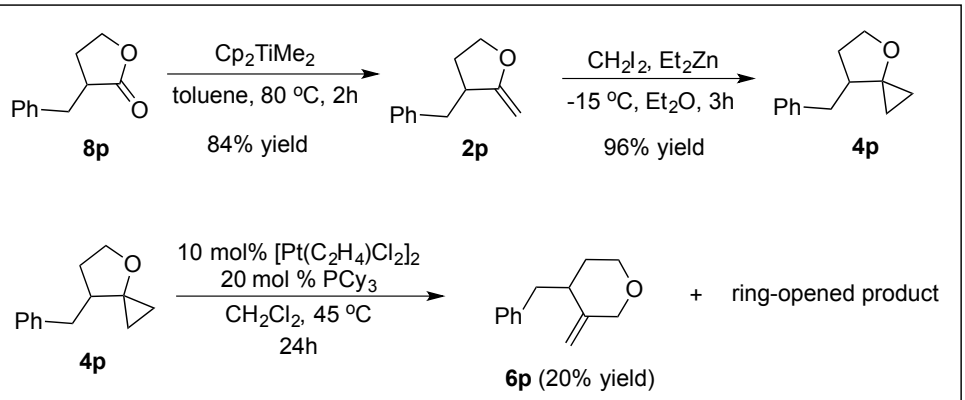


Scheme 27. Proposed mechanism for the Pt(II)-catalyzed expansion of spirocyclopropyloxetanes to 3-methylenetetrahydrofurans. Key mechanistic feature involves the formation of platinacyclobutane and Pt-allyl complexes as intermediates.

Attempts to isolate the platinacyclobutane complex by adding external ligands (e.g. pyridine, bipyridine) used previously in the crystallization of platinacyclobutanes[37a] were not successful. In most cases ring expansion to 3-methylenetetrahydrofuran was still the outcome.

The facile isomerization of the platinacyclobutane intermediate is likely triggered by the favorable ring opening of the strained oxetane ring. We hypothesized that spirocyclopropyltetrahydrofuran **4p** might provide a stable platinacyclobutane complex (Scheme 28). THF **4p** was easily prepared in high yields from methylenenation of lactone **8p** followed by cyclopropanation. However, when **4p** was treated with catalytic amounts of Zeise's dimer, complete conversion to form the ring expanded 3-methylentetrahydropyran **6p** and several ring-opened products were obtained. This result suggests that the regioselective

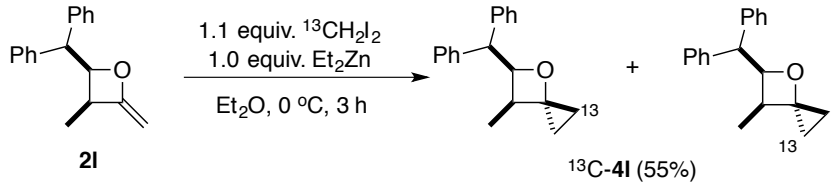
oxidative addition of Pt(II) to the cyclopropane is not altered by the increase in ring size of the oxygen-containing heterocycle.



8p **2p** **4p** **4p** **6p** (20% yield)

Scheme 28. Preparation and reaction of spirocyclopropyltetrahydrofuran **4p**.

To gain insight on the unexpected outcome of spirocyclopropyloxetanes with *cis*-substituents on the oxetane, ^{13}C-labeling experiments were again conducted. ^{13}C-Labeled *cis*-spirocyclopropyloxetane ^{13}C-**4l** was obtained as a pair of isotopic stereoisomers from the cyclopropanation of *cis*-methyleneoxetane **10l** (Scheme 29). The ^{13}C-labeled *cis*-spirocyclopropyloxetane was treated with a stoichiometric amount of Zeise's dimer under the same conditions as used for *trans*-isomer ^{13}C-**4h**, and the reaction was monitored by ^{13}C DEPT NMR.



2l ^{13}C-**4l** (55%)

Scheme 29. Synthesis of C-13 labeled spirocyclopropyloxetane ^{13}C-**4l**.

Somewhat unexpectedly, intermediate peaks analogous to those from ^{13}C-**4h** were observed for a span of 3 h. Specifically, peaks at 8.65 and 13.00 ppm (region **A**, Figure 8) correspond to platinacyclobutanes ^{13}C-**21** with Pt satellites ($^{1}J_{Pt\text{-}^{13}C}$ values of 622.6 and 556.3 Hz, respectively). Likewise, similar to results with ^{13}C-**4h**, isotopomer peaks were observed at

49.4 ppm (region **B**) with a $^{1}J_{Pt\text{-}^{13}C}$ value of 30.9 ($J_{P\text{-}^{13}C}$ = 38.8 Hz) and at 113.6 ppm (region **B'**) with a $^{1}J_{Pt\text{-}^{13}C}$ value of 32.4. These shifts correspond to Pt-η^1-allyl intermediates ^{13}C-**22B** and ^{13}C-**22B'**, respectively. As with the unresolved intermediate peaks observed in the reaction of *trans*- spirocyclopropyloxetanes ^{13}C-**4h**, peaks at around 66 and 68 ppm, which could correspond to Pt-η^3-allyl intermediates,[46,48] were also observed. In contrast to the reaction outcome from ^{13}C-**4h**, *cis*-spirocyclopropyloxetanes ^{13}C-**4l** gave allyl chloride ^{13}C-**11** and 3-methylenetetrahydrofuran ^{13}C-**6l** as the major and minor products, respectively. As a reference, unlabeled *cis*-oxaspirohexane **4l** was also treated with a stoichiometric amount of Ziese's dimer. Allyl chloride **11** was obtained as the major product in 52% yield, and 3-methylenetetrahydrofuran **6l** was obtained in 16% yield (Scheme 30).

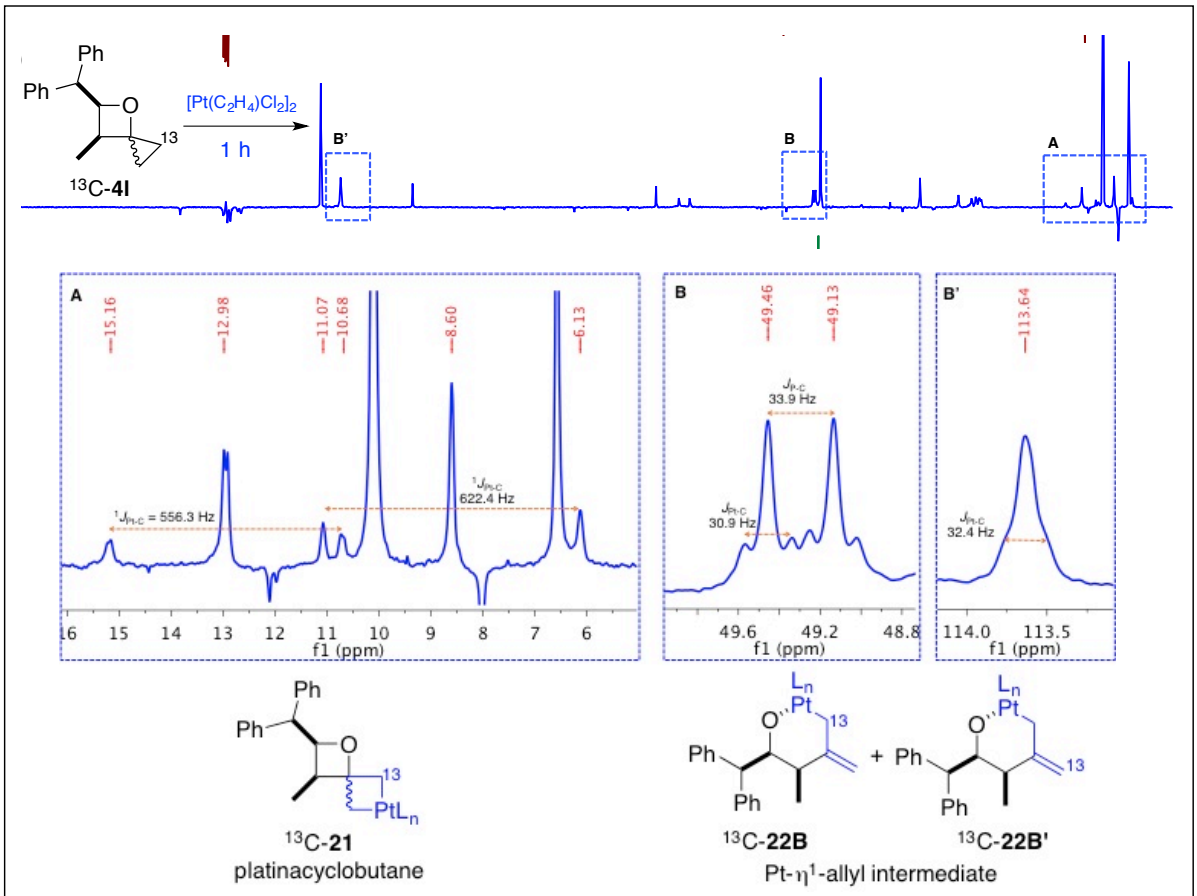
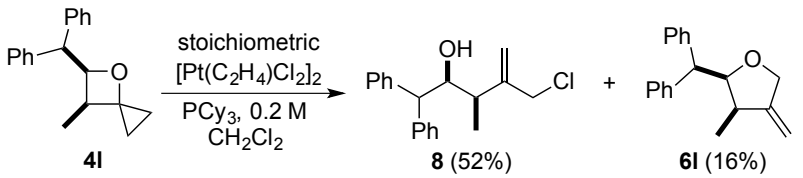
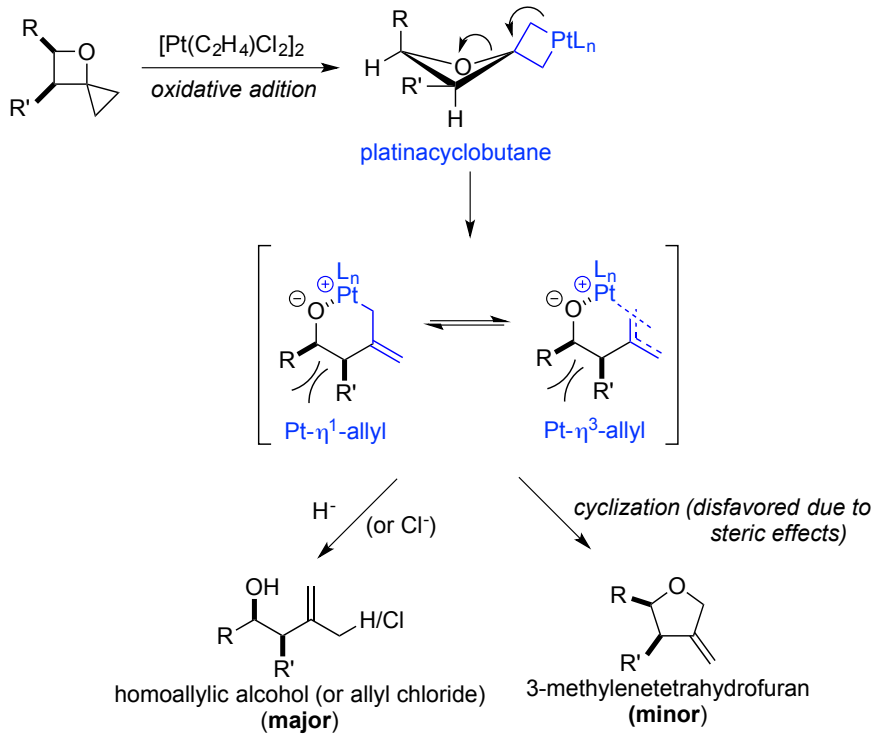


Figure 8. ^{13}C DEPT NMR monitoring showing the regions of ^{13}C labeled carbon peaks observed as intermediates from the reaction of ^{13}C-**4l** with Zeise's dimer: (A) ^{13}C peaks for platinacyclobutane intermediate ^{13}C-**21** (as a pair of ^{13}C-labeled isotopic stereoisomers), and (B) ^{13}C peaks for Pt-η^1-allyl intermediate ^{13}C-**22** as isotopomeric mixture.



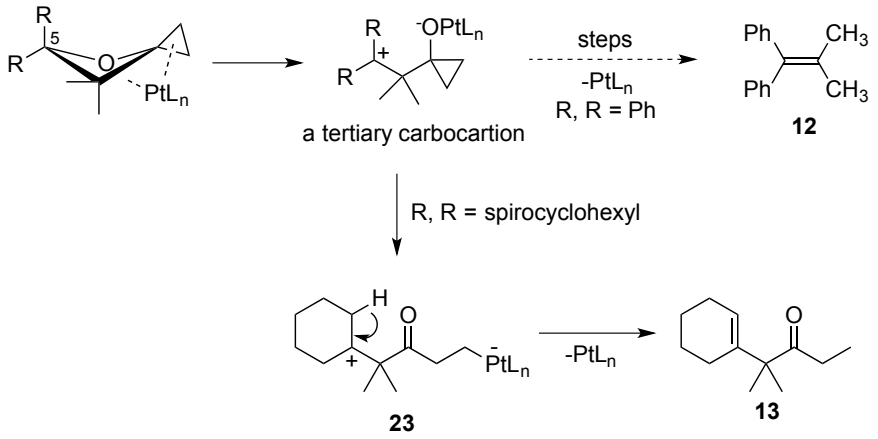
Scheme 30. Reaction of *cis*-spirocyclopropyloxetane **4l** with stoichiometric amount of Zeise's dimer.

Results from the ^{13}C labeling studies with *cis* isomer ^{13}C-**4l** demonstrate that the initial intermediates involved in the reactions of *cis*-spirocyclopropyloxetanes with Zeise's dimer are identical to those observed with the *trans*- spirocyclopropyloxetanes, even though the product distribution is different. Initial oxidative addition of cyclopropane to Pt to form platinacyclobutanes is followed by ring-opening to Pt-allyl intermediates (Scheme 31). However, rather than cyclization, the allyl intermediate reacts with a chloride ion to form allyl chloride **8**. For **4k** the Pt-allyl intermediate undergoes reductive elimination to give homoallyl alcohol **9** (Scheme 21). The contrasting outcome (reduction vs. substitution) between *cis*-spirocyclopropyloxetanes **4k** and **4l** requires that the allyl intermediates undergo different reactions. For the reaction of **4k** the isolation of a significant amount of dienone **10** (which must arise from **4k**, rather than a Pt-allyl intermediate) suggests a hydride source. Steric encumbrance could prevent **4l** from providing a hydride. We propose that the low reactivity of the *cis*-isomers is due to steric effects that disfavor the conformation required for the formation of 3-methylenetetrahydrofurans, which leaves the door open for alternative pathways.



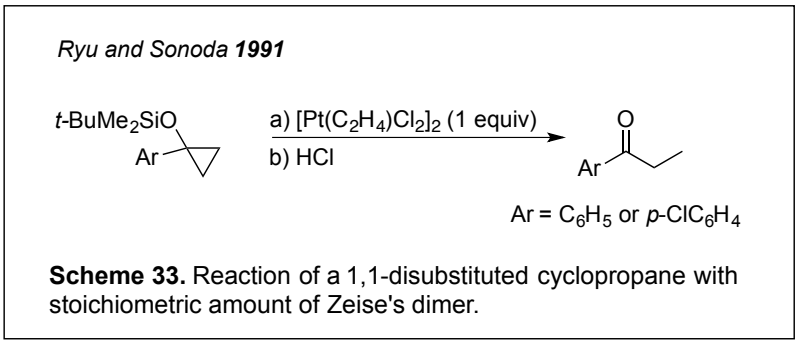
Scheme 31. Proposed mechanism for the Pt(II)-catalyzed expansion and opening of *cis*-spirocyclopropyloxetanes. Key mechanistic feature involves the formation of platinacyclobutane and Pt-allyl complexes as intermediates. Cyclization to of the allyl intermediates to 3-methylenetetrahydrofuran is disfavored pressumably due to sterric effects associated with the transition state leading to the cyclic THF product.

For the case of 5,5-disubstituted spirocyclopropyloxetanes, we postulate a rearrangement where Pt mediated bond breaking of the C-O bond in the oxetane ring occurs before cleavage of the cyclopropane (Scheme 32). This is presumably due to the formation of a tertiary carbocation that ultimately leads to **12** or **13**. The zwitterionic β-platinum(II) ketone intermediate **23** is analogous to the intermediates proposed[39] and the platinum complex[51] isolated by Ryu and Sonoda during their mechanistic investigation of the Pt-catalyzed isomerization of silyloxycyclopropane to allyl silylethers (see Scheme 14).



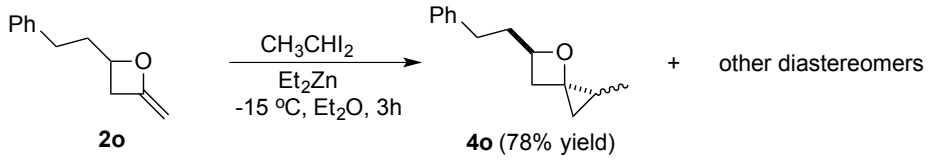
Scheme 32. Rationalization of the different outcome of 5,5-disubstituted spirocyclopropyloxetanes.

It could be argued that the regioselective formation of platinacyclobutane through the methylenes of the cyclopropane is governed by steric effects. Indeed, most reports of the reaction of Zeise's dimer with 1,1-disubstituted cyclopropanes give products consistent with initial substitution into this less hindered C-C bond.[37a] However, earlier reports of the reaction of Zeise's dimer with silyloxycyclopropanes had included 1,1-disubstituted compounds. For example, silyloxycyclopropanes were converted to ketones in the presence of Zeise's dimer (Scheme 33).[51] Formation of the ketone requires cleavage of the oxygen-substituted cyclopropane C-C bond. Thus, our initial expectation of platinacyclobutane formation through C-C bond adjacent to the oxetane was warranted. Nevertheless, it seemed worthwhile to examine the effect of placing additional substitution on the cyclopropane.

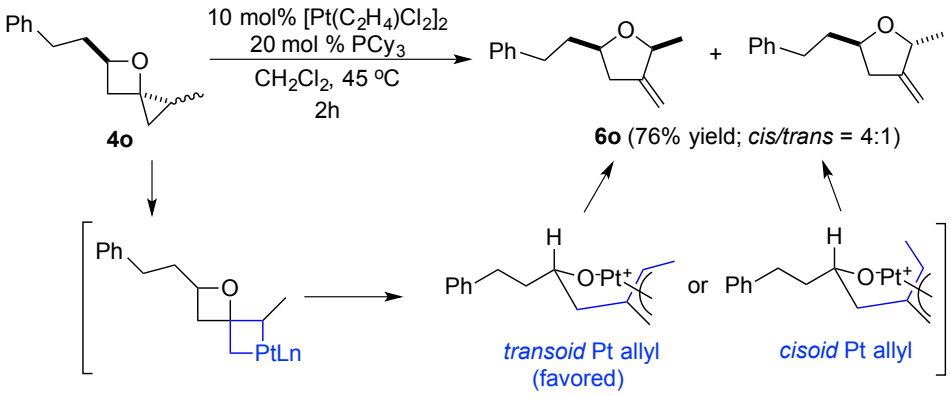


Scheme 33. Reaction of a 1,1-disubstituted cyclopropane with stoichiometric amount of Zeise's dimer.

A spirocyclopropyloxetane bearing a methyl substituent at the cyclopropyl moiety was prepared by the cyclopropanation of **10o** using diodoethane (Scheme 34). This provided **4o** in 78% yield (isolated as a single enantiomeric pair, but with the relative stereochemistries unknown). Other diasteromeric products were also obtained as an inseparable mixture in trace amounts. 1-Methyl substituted spirocyclopropyloxetane **4o** was treated with Zeise's dimer, and 3-methylenetetrahydrofuran **6o**, isolated in 76% yield (4:1 *cis*/*trans*), resulted (Scheme 35). The observed complete regioselectivity and formation of *cis* isomer as the major product further supports the intermediacy of a Pt-allyl intermediate that undergoes a 5-*exo* cyclization mode via the more stable *transoid* Pt-allyl intermediate. Such outcomes were observed in cyclizations of related Pd-allyl systems with O-nucleophiles.[52] These results demonstrate that an additional alkyl substituent on the cyclopropane did not alter the outcome of the reaction, confirming that the regioselectivity can not be entirely explained by steric effects.



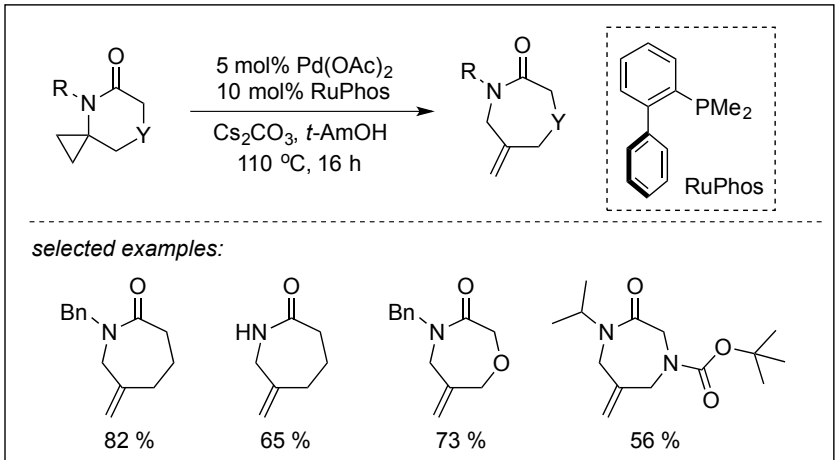
Scheme 34. Preparation of spirocyclopropyloxetane **4o** having a methyl substituent on the cyclopropane.



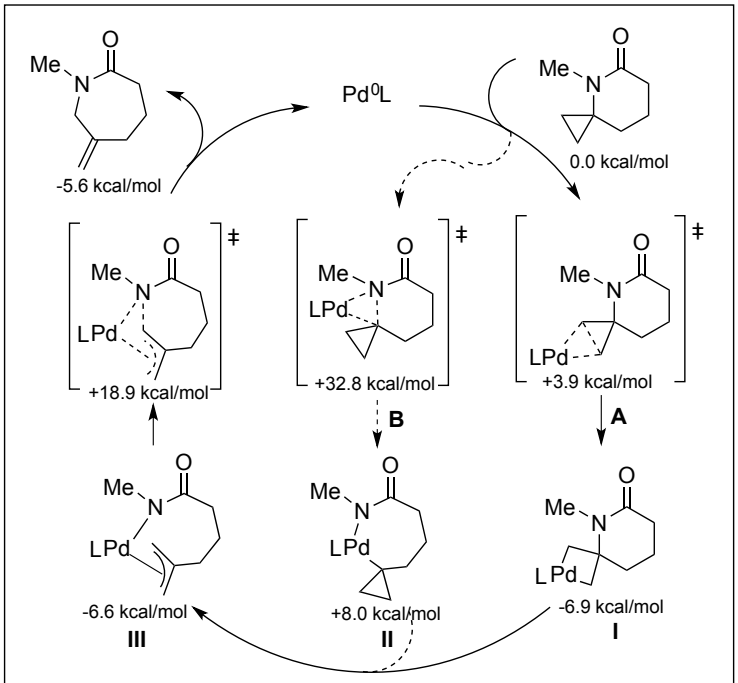
Reaction conditions: 1.0 mmol scale, 10 mol % **3**, 20 mol % PCy_3, 0.5 M in CH_2Cl_2.
Cis/*trans* ratio was based from ^1H NMR analysis of the crude mixture.

Scheme 35. Reaction of spirocyclopropyloxetane **4o** with catalytic Zeise's dimer and proposed mechanism on the observed regio- and diastereoselectivities.

René and coworkers recently described an analogous cyclopropane activation strategy for the ring expansion of spirocyclopropyl lactams to methylenecaprolactams under palladium catalysis (Scheme 36).[53] In contrast to our mechanistic experiments, they have supported their work by computational studies. Calculations on possible mechanistic pathways suggest an initial oxidative addition of Pd(0) to the distal carbon-carbon bond of cyclopropane to form intermediate pallacyclobutane **I** (Scheme 37, path A). The formation of palladacyclobutane **I** is highly energetically favored over oxidative addition of Pd(0) to the C–N bond of the lactam to form intermediate **II**. Rearrangement of **I** to Pd-allyl complex **III** followed by cyclization would provide the methylenecaprolactam product. However, when this reaction was conducted using Zeise's dimer as the catalyst, no reaction was observed.



Scheme 36. Pd-catalyzed ring expansion of spirocyclopropyl lactams to methylenelactams.



Scheme 37. Proposed mechanism for Pd-catalyzed ring expansion of spirocyclopropyl lactams to methylenelactams based from computationally calculated mechanistic pathways.

1.4 Conclusion

A novel Pt(II)-catalyzed expansion of spirocyclopropyloxetanes to 3-methylenetetrahydrofurans has been discovered. In this work, we highlight the first detection of alkoxy-substituted platinacyclobutane intermediates. In contrast to previous reactions with oxygen-substituted cyclopropanes, where oxidative addition to Pt occurred adjacent to the C-O bond, regioselective platinacyclobutane formation through the distal methylene carbons of the cyclopropane ring resulted. The key platinacyclobutane and Pt-allyl intermediates were observed by ^{13}C NMR studies using ^{13}C-labeled spirocyclopropyloxetanes. In particular, these studies clarified that, although outcomes with *cis*-5,6-disubstituted oxaspirohexanes were different than those with *trans*-5,6-disubstituted (or 5- or 6-substituted) oxaspirohexanes, the intermediates were identical. A spirocyclopropyloxetane bearing a substituent on the cyclopropane ring was also efficiently converted to a 3-methylenetetrahydrofuran with complete regioselectivity.

1.5 Experimental

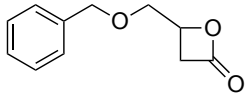
1.5.1 General Information

All moisture sensitive reactions were run in a flame-dried flask under nitrogen. All solvents were dried over CaH_2 or 4 Å molecular sieves. Tetrahydrofuran (THF) was dried using J. C. Meyer Solvent Dispensing System (SDS) and dispensed under N_2. Deuterated chloroform ($CDCl_3$), and methylene chloride (CD_2Cl_2) were dried over 4 Å molecular sieves. Commercially available reagents were purchased from Aldrich, Acros, Alfa Aesar or TCI America and used without further purification. Zeise's dimer was purchased from Strem chemicals.

All ^1H NMR experiments were recorded using a Bruker AVANCE 300, 400 or 500 MHz spectrometer. All ^{13}C NMR experiments were recorded using a Bruker AVANCE 75, 100 or 125 MHz spectrometer. Chemical shifts (δ) are given in ppm, and coupling constants (J) are given in Hz. The 7.26 resonance of residual $CHCl_3$ for proton spectra and the 77.23 ppm resonance of $CDCl_3$ for carbon spectra were used as internal references. High-resolution mass spectra (HRMS) were obtained using DART AccuTOF or JEOL JMS-AX505HA mass spectrometers. Reaction progress was monitored by thin layer chromatography (TLC) performed on glass plates coated with silica gel UV254. Visualization was achieved by ultraviolet light (254 nm), 0.5% $KMnO_4$ in 0.1 M aqueous NaOH solution and/or 5% phosphomolybdic acid in ethanol. Column chromatography was performed using silica gel, 40 microns flash silica.

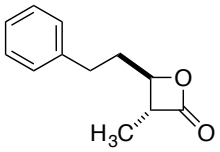
1.5.2 Preparation of β-lactones

Known β-lactones **8c, i**, and **n** were prepared by following literature procedures. Spectral data are in accordance with the literature references.



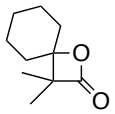
8c

4-Benzyloxymethyloxetan-2-one (8c)[54] was obtained as a colorless oil (1.10 g, 41%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.60 (m, 3H), 3.74 (m, 2H), 3.40 (m, 2H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 167.8, 137.5, 128.5, 127.9, 127.7, 73.6, 69.4, 69.3, 39.6.



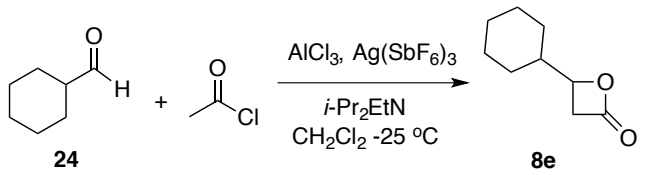
8i

***trans*-3-Methyl-4-(2-phenylethyl)-oxetan-2-one (8i)**[55] was obtained as a pale yellow oil (1.12 g, 47%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.17 (m, 5H), 4.16 (ddd, *J* = 7.5, 5.9, 4.0 Hz, 1H), 3.20 (dq, *J* = 7.5, 4.0 Hz, 1H), 2.77 (m, 2H), 2.13 (m, 2H), 1.32 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 139.9, 128.5, 128.2, 126.3, 78.6, 50.8, 35.6, 31.4, 12.5.



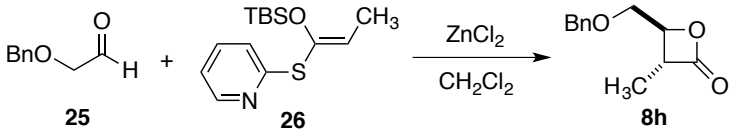
8n

3,3-Dimethyloxetan-2-one-4-spirocyclohexane (8n)[56] was obtained as needle-like white crystals (2.12 g, 51%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95−1.91 (m, 2H), 1.68−1.60 (m, 7H), 1.29 (br s, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 85.3, 54.5, 32.5, 24.9, 22.8, 18.2.



24 8e

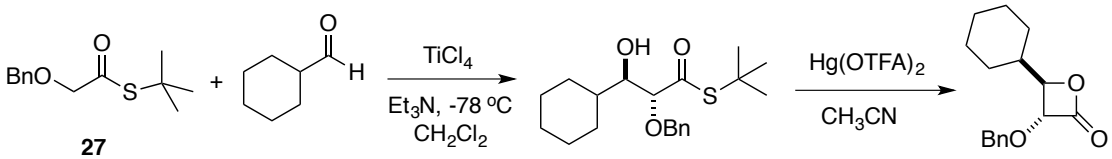
[57]**4-Cyclohexyloxetan-2-one (8e).** A solution of $Ag(SbF_6)_3$ (9.10 g, 26.6 mmol) in dry CH_2Cl_2 (60 mL) was added to a solution of $AlCl_3$ (1.18 g, 8.88 mmol) and *i*-Pr_2EtN (4.60 mL, 26.6 mmol) in CH_2Cl_2 (60 mL) at −25 °C under N_2 to form a heterogeneous mixture. *i*-Pr_2EtN (7.70 mL, 44.4 mmol), acetyl chloride (4.70 mL, 66.5 mmol) and a solution of cyclohexylcarboxaldehyde (5.00 g, 44.3 mmol) in CH_2Cl_2 (13 mL) were added, and the resulting mixture was stirred at −25 °C for 4 h. The reaction mixture was then filtered through a pad of Celite, and the Celite was washed with CH_2Cl_2 (3 x 5 mL). The filtrate was then concentrated to give a pale yellow oil. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10) afforded 4-cyclohexyloxetan-2-one (**8e**) as a colorless oil (4.9 g, 72%):[10] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (m, 1H), 3.43 (dd, *J* = 16.3, 5.8 Hz, 1H), 3.11 (dd, *J* = 16.3, 4.4 Hz, 1H), 1.97−1.52 (m, 6H), 1.39−0.90 (m, 5H).



25 26 8h

***trans*-4-Benzyloxymethyl-3-methyloxetan-2-one (8h).** Anhydrous $ZnCl_2$ (5.45 g, 39.9 mmol) was freshly fused at ~0.5 mmHg. After cooling to ambient temperature CH_2Cl_2 (140 mL) was added, and the $ZnCl_2$ was broken up into small pieces with a spatula. 2-Benzyloxyacetaldehyde (**25**)[58] (4.00 g, 26.6 mmol) dissolved in dry CH_2Cl_2 (20 mL) was then added, resulting in a cloudy solution. After 15 min of stirring, TBS-thiopyridylketene acetal **26**[11] (8.25 g, 29.3 mmol) in dry CH_2Cl_2 (20 mL) was added and the reaction mixture was stirred for 45 h at rt. After completion of the reaction, freshly made phosphate buffer (pH = 7, 25 mL) was added, and the resulting mixture was stirred vigorously for 15 min. It was then filtered

through Celite, and the Celite was washed with CH_2Cl_2 (3 x 10 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$), and $CuBr_2$ (8.50 g, 38.1 mmol) was added. The reaction mixture was stirred for 1.5 h at rt. It was then filtered through a pad of Celite, and the Celite was washed with CH_2Cl_2 (3 x 10 mL). The filtrate was washed with saturated aqueous K_2CO_3 (15 mL), then brine (15 mL). The organic layer was dried ($MgSO_4$) and concentrated to give a sticky oil. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10) yielded *trans*-4-benzyloxymethyl-3-methyloxetan-2-one (**9h**) as a colorless oil (3.85 g, 70%):[44a] IR (neat) 3064, 3031, 2975, 1936, 2875, 1822, 1454, 1120, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.26 (m, 5H), 4.61 (d, *J* = 12.6 Hz, 1H), 4.58 (d, *J* = 12.6 Hz, 1H), 4.31 (ddd, *J* = 4.0, 4.0, 4.0 Hz, 1H), 3.79 (dd, *J* = 11.8, 3.7 Hz, 1H), 3.72 (d, *J* = 11.1, 4.7 Hz, 1H), 3.58 (dq, *J* = 7.7, 4.4 Hz, 1H), 1.39 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 137.6, 128.7, 128.1, 127.9, 77.5, 73.9, 69.3, 47.6, 12.4; HRMS (ESI) calcd for $C_{12}H_{15}O_3$ $(M + H)^+$ *m/z* 207.1021, found 207.1011.

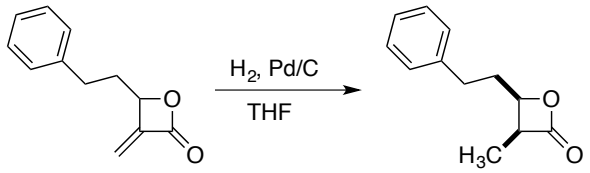


27 **28** **8j**

[59]**(2*R**,3*R**)-2-Benzyloxy-3-cyclohexyl-3-hydroxy-1-*S*-*tert*-butylthiopropiolate (28).** 2-Benzyloxy-*S*-*tert*-butyl-1-thioacetate (**27**)[60] (4.25 g, 17.8 mmol) was dissolved in dry CH_2Cl_2 (60 mL) under nitrogen and cooled to −78 °C. A solution of $TiCl_4$ (1 M in CH_2Cl_2, 17.8 mL, 17.8 mmol) was added to the flask drop-wise over 10 min. After 5 min Et_3N (5.00 mL, 35.7 mmol) was added. The solution was stirred at −78 °C for 30 min, and then a solution of cyclohexylcarboxylaldehyde (2.00 g, 17.8 mmol) in CH_2Cl_2 (18 mL) was added drop-wise. The reaction was stirred at −78 °C for 4 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL), and the resulting slurry was filtered through Celite. The Celite was

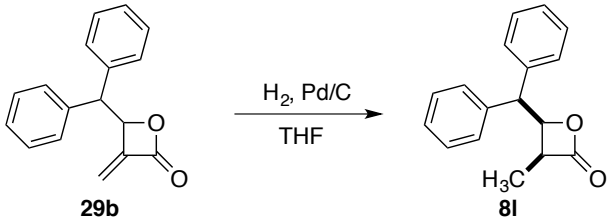
washed with CH_2Cl_2 (3 x 5 mL). The organic and aqueous layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 85:15) afforded (2*R**,3*R**)-2-benzyloxy-3-cyclohexyl-3-hydroxy-1-*S*-*tert*-butylthiopropiolate (**28**) as a colorless oil (3.18 g, 51%):[44a] IR (neat) 3031, 2912, 2853, 1826, 1728, 1452, 1115, 892 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H), 4.81 (d, *J* = 11.4 Hz, 1H), 4.45 (d, *J* = 11.4 Hz, 1H), 3.85 (d, *J* = 6.4 Hz, 1H), 3.63 (ddd, *J* = 4.8, 4.8, 4.8 Hz, 1H) 2.33 (d, *J* = 4.9 Hz, 1H), 1.70 (m, 2H), 1.63 (m, 4H), 1.51 (s, 9H), 1.30−1.03 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.4, 137.1, 128.6, 128.3, 128.2, 85.5, 76.6, 73.5, 47.6, 39.2, 29.8, 26.7, 26.5, 26.4, 26.1; HRMS (ESI) calcd for $C_{20}H_{31}O_3S$ $(M + H)^+$ *m/z* 351.1994, found 351.1998.

***trans*-3-Benzyloxy-4-cyclohexyloxetan-2-one (8j).** (2*R**,3*R**)-2-Benzyloxy-*S*-*tert*-butyl-3-cyclohexyl-3-hydroxy-1-thiopropiolate (**28**) (2.00 g, 5.71 mmol) was dissolved in dry CH_3CN (200 mL) under nitrogen at rt. $Hg(OTFA)_2$ (2.74 g, 6.41 mmol) was added to this solution at once. The resulting reaction mixture was quickly immersed into a pre-heated oil-bath (50 °C). After 5 minutes the mixture was filtered through a pad of Celite which was washed with CH_2Cl_2 (3 x 5 mL). The filtrate was then concentrated to give a pale brown oil. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 92:8) afforded *trans*-3-benzyloxy-4-cyclohexyloxetan-2-one (**8j)** as a colorless oil (0.68 g, 46%):[44a] IR (neat) 3064, 3032, 2928, 2854, 1833, 1451, 1146, 865, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.32 (m, 5H), 4.81 (d, *J* = 11.6 Hz, 1H) 4.66 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 3.6 Hz, 1H), 4.22 (dd, *J* = 8.5, 3.6 Hz, 1H), 1.87 (m, 1H) 1.79−1.50 (m, 5H), 1.28−1.13 (m, 3H), 1.08−0.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 136.4, 128.7, 128.4, 128.1, 83.8, 83.6, 72.5, 40.1, 28.4, 27.1, 25.9, 25.3, 25.1; HRMS (ESI) calcd for $C_{16}H_{21}O_3$ $(M + H)^+$ *m/z* 261.1491, found 261.1465.



29a **8k**

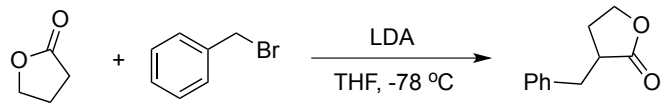
***cis*-3-Methyl-4-(2-phenylethyl)oxetan-2-one (8k).** 3-Methylene-4-(2-phenylethyloxetan-2-one (**29a**)[61] (1.88 g, 10 mmol) and 10% Pd on carbon (0.30 mmol, 0.32 g) were mixed in dry THF (10 mL) under a N_2 atmosphere. The reaction vessel was purged with H_2 for 10 min. The reaction mixture was stirred at rt for 2 h under a balloon filled with H_2. The crude mixture was filtered through a pad of Celite. The Celite was washed with CH_2Cl_2 (3 x 10 mL), and the filtrate was concentrated to give a pale yellow oil. ^{1}H NMR analysis of the crude product showed a diastereomer ratio of 10:1 (*cis*:*trans*). Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 92:8) afforded *cis*-4-(2-phenylethyl)-3-methyloxetan-2-one (**8k**) as a pale yellow oil (1.67 g, 88%):[62] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5H), 4.57 (ddd, *J* = 4.5, 4.5, 4.5 Hz, 1H), 3.74 (dq, *J* = 14.6, 7.4 Hz, 1H), 2.90 (ddd, *J* = 14.2, 5.3, 5.3 Hz, 1H), 2.73 (m, 1H), 2.06 (m, 2H), 1.28 (d, *J* = 7.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 140.4, 128.5, 128.4, 126.2, 74.6, 47.1, 31.8, 31.4, 8.0.



29b **8l**

***cis*-4-Benzhydryl-3-methyloxetan-2-one (8l).** 4-Benzhydryl-3-methyleneoxetan-2-one (**29b**)[61] (4.0 mmol, 1.0 g) and 10% Pd on carbon (0.12 mmol, 0.12 g) were mixed in dry THF (4 mL) under a N_2 atmosphere. The reaction vessel was purged with H_2 for 10 min. The reaction mixture was stirred at rt for 2 h under a balloon filled with H_2. The crude mixture was filtered through a pad of Celite. The Celite was washed with CH_2Cl_2 (3 x 10 mL), and the

filtrate was concentrated to give a pale yellow oil. ^{1}H NMR analysis of the crude product showed a diastereomer ratio of 20:1.7 (*cis*:*trans*). Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 92:8) afforded *cis*-4-benzhydryl-3-methyloxetan-2-one (**8l**) as a pale yellow oil (0.91g, 88%): IR (neat) 3054, 3035, 2950, 1820, 1450, 1144 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.21 (m, 10H), 5.28 (dd, *J* = 11.2, 6.1, 1H), 4.28 (d, *J* = 11.2, 1H), 3.86 (m, 1H), 1.12 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 140.8, 139.6, 129.2, 128.8, 128.4, 128.0 127.5, 127.3, 76.9, 51.5, 48.0, 9.1; HRMS (ESI) calcd for $C_{17}H_{17}O_2$ $(M + H)^+$ *m/z* 253.1229, found 253.1233.

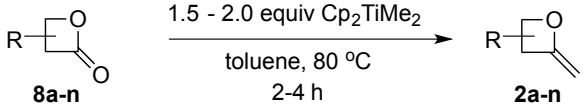


8p

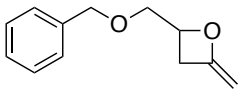
3-Benzyltetrahydrofuran-2-one (8p). *n*-Buli (6.6 mL, 16.5 mmol, 2.5 M in hexane) was added to diisopropylamine (1.67 g, 16.5 mmol) in THF (20 mL) under N_2 at –78 °C. The resulting solution was stirred for 20 min. γ-Butyrolactone (1.29 g, 15.0 mmol) was added neat over 20 min; then benzyl bromide (2.57 g, 15.0 mmol) in THF (10 mL) was added dropwise over 20 min. The resulting reaction mixture was stirred for 1.5 h at –78 °C. The reaction was quenched with saturated ammonium chloride and extracted with diethyl ether (50 mL x 3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 85:15), providing 3-benzyltetrahydrofuran-2-one (**8p**) as a colorless oil (2.06 g, 78%):[63] δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.16 (m, 2H), 7.12–7.07 (m, 3H), 4.05 (ddd, *J* = 8.8, 8.8, 3.0 Hz, 1H), 3.97 (ddd, *J* = 9.4, 9.4, 6.7 Hz, 1H), 3.09 (dd, *J* = 13.5, 3.9 Hz, 1H), 2.70 (ddd, *J* = 13.5, 9.2, 4.2 Hz, 1H), 2.61 (dd, *J* = 13.5, 9.3 Hz, 1H), 2.12−2.04 (m, 1H), 1.88−1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 138.4, 128.8, 128.5, 126.6, 66.4, 40.9, 35.9, 27.8.

1.5.3 Preparation of 2-methyleneoxetanes

General procedure for the preparation of 2-methyleneoxetanes

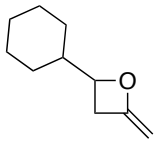


A solution of dimethyltitanocene[64] (0.5 M in toluene, 1.5-2 equiv) and *β*-lactone (1 equiv) was stirred in the dark at 80 °C under N_2. The progress of the reaction was monitored over a period of 2-4 h by TLC until the disappearance of the starting material. The cooled reaction mixture was added to petroleum ether (10 volumes) and stirred overnight. The resulting mixture was filtered through a pad of Celite, washing with petroleum ether until the filtrate was colorless. The filtrate was concentrated to about one-third of the original volume of toluene, and the residue was purified by flash column chromatography on silica gel (deactivated by 4% Et_3N in petroleum ether).



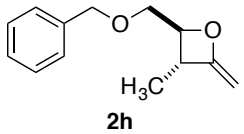
2c

4-Benzyloxymethyl-2-methyleneoxetane (2c). 4-Benzyloxymethyl-2-methyleneoxe-tane (**10c**) was prepared from 4-benzyloxymethyloxetan-2-one (**8c**) (0.50 g, 2.6 mmol) using 1.5 equiv. of dimethyltitanocene. Purification by flash chromatography on silica gel (petroleum ether /EtOAc/Et_3N, 99:0.5:0.5) afforded 4-benzyloxymethyl-2-methyleneoxetane (**2c**) as a pale yellow oil (0.35 g, 70%):[44b] IR (neat) 3100, 2926, 1691, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 3H), 7.28 (m, 2H), 4.91 (dddd, *J* = 19.1, 6.9, 5.1, 5.1 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.16 (ddd, *J* = 3.5, 2.4, 2.4 Hz, 1H), 3.78 (ddd, *J* = 3.6, 1.8, 1.8 Hz, 1H), 3.71 (dd, *J* = 11.3, 5.0, 1H), 3.70 (dd, *J* = 11.3, 1.5 Hz, 1H), 3.20 (dddd, *J* = 14.8, 7.0, 1.2, 1.2 Hz, 1H), 3.03 (dddd, *J* = 14.8, 5.2, 2.0, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 138.1, 128.6, 128.0, 80.4, 77.6, 73.8, 71.9, 31.1; HRMS (ESI) calcd for $C_{12}H_{15}O_2$ $(M + H)^+$ *m/z* 191.1072, found 191.1058.



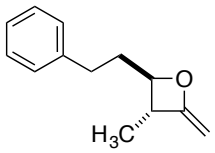
2e

4-Cyclohexyl-2-methyleneoxetane (2e). 4-Cyclohexyl-2-methyleneoxetane (**2e**) was prepared from 4-cyclohexyloxetan-2-one (**8e**) (1.0 g, 6.5 mmol) using 2.0 equiv. of dimethyltitanocene. Purification by flash chromatography on silica gel (petroleum ether /Et_3N, 99.5.0.5) afforded 4-cyclohexyl-2-methyleneoxetane (**2e**) as a pale yellow oil (0.48 g, 48%):[18] ^1H NMR (300 MHz, $CDCl_3$) δ 4.39 (m, 1H), 4.07 (m, 1H), 3.69 (m, 1H), 3.12 (m, 1H), 2.83 (m, 1H), 1.89 (m, 1H), 1.66 (m, 5H), 1.18 (m, 3H), 0.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 83.0, 79.5, 43.2, 32.4, 27.9, 26.5, 26.4, 25.7, 25.4.



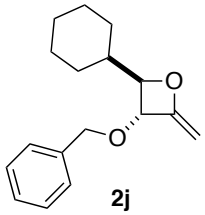
2h

***trans*-4-Benzyloxymethyl-3-methyl-2-methyleneoxetane (2h).** *trans*-4-Benzyloxy-methyl-3-methyl-2-methyleneoxetane (**2h**) was prepared from *trans*-4-benzyloxy-methyl-3-methyloxetan-2-one (**8h**) (0.50 g, 2.4 mmol) using 2.5 equiv. of dimethyltitanocene. Purification by flash chromatography on silica gel (petroleum ether /EtOAc/Et_3N, 95.5:4:0.5) afforded *trans*-4-benzyloxymethyl-3-methyl-2-methylene-oxetane (**2h**) as a pale yellow oil (0.38 g, 75%): IR (neat) 3031, 2934, 2878, 1715, 1496, 1454, 1359, 1275, 1114, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.28 (m, 5H), 4.62 (m, 2H), 4.57 (ddd, *J* = 4.7, 4.7, 4.7 Hz, 1H), 4.13 (dd, *J* = 3.6, 2.3 Hz, 1H), 3.79 (dd, *J* = 3.6, 1.7 Hz, 1H), 3.75−3.65 (m, 2H), 3.30 (m, 1H), 1.30 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 138.1, 128.5, 127.8, 112.1, 85.5, 78.4, 73.7, 71.4, 38.6, 16.5; HRMS (ESI) calcd for $C_{13}H_{17}O_2$ $(M + H)^+$ *m/z* 205.1229, found: 205.1220.



2i

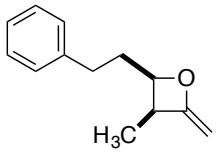
***trans*-3-Methyl-2-methylene-4-(2-phenylethyl)oxetane (2i).** *trans*-3-Methyl-2-methylene-4-(2-phenylethyl)oxetane (**2i**) was prepared from *trans*-3-methyl-4-(2-phenylethyl)oxetan-2-one (**8i**) (0.56 g, 2.9 mmol) using 2.0 equiv. of dimethyltitanocene. Purification by flash chromatography on silica gel (petroleum ether /EtOAc/Et_3N, 95.5:4:0.5) afforded *trans*-3-methyl-2-methylene-4-(2-phenylethyl)oxetane (**2i**) as a pale yellow oil (0.41 g, 74%):[24a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.22 (m, 3H), 4.39 (ddd, *J* = 7.7, 4.0, 4.0 Hz, 1H), 4.09 (dd, *J* = 3.4, 2.4 Hz, 1H), 3.75 (dd, *J* = 3.6, 1.7 Hz, 1H), 3.05 (m, 1H), 2.76 (ddd, *J* = 14.0, 9.5, 5.7 Hz, 1H), 2.65 (ddd, *J* = 14.1, 9.1, 7.1 Hz, 1H), 2.16 (m, 1H), 2.01 (m, 1H), 1.24 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 141.2, 128.7, 128.6 126.3, 86.7, 78.1, 42.2, 37.4, 30.9, 16.8.



2j

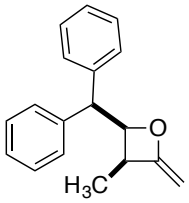
***trans*-3-Benzyloxy-4-cyclohexyl-2-methyleneoxetane (2j).** *trans*-4-Benzyloxy-3-cyclohexyl-2-methyleneoxetane (**2j**) was prepared from *trans*-3-benzyloxy-4-cyclohexyloxetan-2-one (**8j**) (0.42 g, 1.6 mmol) using 1.5 equiv. of dimethyltitanocene. Purification by flash chromatography on silica gel (petroleum ether /Et_2O/Et_3N, 95.5:4:0.5) afforded *trans*-4-benzyloxy-3-cyclohexyl-2-methyleneoxetane (**2j**) as a clear oil (0.23 g, 57%):[44a] IR (neat) 2927, 2853, 1726, 1451, 1119, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (4H), 7.32−7.25 (m, 1H), 4.61 (s, 2H), 4.57 (dd, *J* =1.7, 1.7 Hz, 1H), 4.42 (dd, *J* = 8.2, 3.8 Hz, 1H), 4.25 (dd, *J* = 3.3, 1.6 Hz, 1H), 4.01 (dd, *J* = 3.5, 1.0 Hz, 1H), 1.86 (m, 1H), 1.78−1.74 (m, 2H), 1.70−1.63 (m, 2H), 1.60−1.53 (m, 1H), 1.25−1.12 (m, 3H), 1.03−0.92 (m, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 164.2, 137.7, 128.7, 128.2, 128.0, 91.2, 81.7, 77.7, 71.1, 41.1, 28.1, 26.9, 26.4, 25.7, 25.4; HRMS (ESI) calcd for $C_{17}H_{23}O$ $(M + H)^+$ *m/z* 259.1698, found 259.1674.



2k

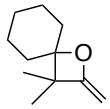
***cis*-3-Methyl-2-methylene-4-(2-phenylethyl)oxetane (2k).** *cis*-3-Methyl-2-methylene-4-(2-phenylethyl)oxetane (**2k**) was prepared from *cis*-4-(2-phenylethyl)-3-methyloxetan-2-one (**8k**) (0.5 g, 2.7 mmol) using 2 equiv. of dimethyltitanocene. Purification by flash chromatography on silica gel (petroleum ether /Et_2O/Et_3N, 97.5:2:0.5) afforded *cis*-3-methyl-2-methylene-4-(2-phenylethyl)oxetane (**2k**) as a pale yellow oil (0.36 g, 72%): IR (neat) 3026, 2924, 2854, 1706, 1603, 1496, 1454, 1180, 1082, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.26 (m, 2H), 7.22−7.18 (m, 3H), 4.80 (ddd, *J* = 9.6, 7.0, 3.9 Hz, 1H), 4.09 (dd, *J* = 3.4, 2.4 Hz, 1H), 3.73 (dd, *J* = 3.4, 1.7 Hz, 1H), 3.55 (m, 1H), 2.81 (ddd, *J* = 14.1, 9.9, 5.1 Hz, 1H), 2.60 (m, 1H), 2.16 (dddd, *J* = 19.1, 14.4, 9.5, 5.2 Hz, 1H), 1.88 (dddd, *J* = 20.8, 10.8, 6.9, 4.0 Hz, 1H), 1.18 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 169.8, 141.5, 128.7, 126.3, 82.4, 78.0, 38.3, 32.8, 31.5, 12.4; HRMS (ESI) calcd for $C_{13}H_{17}O$ (M^+) *m/z* 189.1279, found 189.1268.



2l

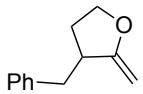
***cis*-4-Benzhydryl-3-methyl-2-methyleneoxetane (2l).** *cis*-4-Benzhydryl-3-methyl-2-methyleneoxetane (**2l**) was prepared from *cis*-4-benzhydryl-3-methyloxetan-2-one (**8l**) (0.15 g, 0.60 mmol) using 2 equiv. of dimethyltitanocene. Purification by flash chromatography on silica gel (petroleum ether/Et_2O/Et_3N, 97.5:2:0.5) afforded *cis*-4-benzhydryl-3-methyl-2-methyleneoxetane (**2l**) as a pale yellow oil (0.12 g, 78%). ^1H NMR (500 MHz, $CDCl_3$) δ

7.05−6.99 (m, 6H), 6.96−6.89 (m, 4H), 5.27 (dd, *J* = 11.2, 6.8 Hz, 1H), 4.14 (d, *J* = 11.2 Hz, 1H), 3.86 (dd, *J* = 3.6, 2.2 Hz, 1H), 3.50 (dd, *J* = 3.6, 1.7 Hz, 1H), 3.37 (m, 1H), 0.78 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 141.6, 140.7, 129.0, 128.8, 128.5, 128.2, 127.0, 127.0, 83.9, 78.4, 51.9, 39.0, 13.4; HRMS (ESI) calcd for $C_{18}H_{18}O$ $(M + H)^+$ *m/z* 251.1435, found 251.1422.



2n

3,3-Dimethyl-2-methylene-1-oxaspiro[3.5]nonane (2n). 3,3-Dimethyl-2-methylene-1-oxaspiro[3.5]nonane (**2n**) was prepared from 3,3-dimethyloxetan-2-one-4-spirocyclohexane (**8n**) (1.5 g, 8.9 mmol) using 2 equiv. of dimethyltitanocene. Purification by flash chromatography on silica gel (petroleum ether/Et_3N, 99.5:0.5) afforded 3,3-dimethyl-2-methylene-1-oxaspiro[3.5]nonane (**2n**) as a pale yellow oil (1.1 g, 70%): IR (neat) 2925, 2859, 1693, 1469, 1368, 1123 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (d, *J* = 3.3 Hz, 1H), 3.62 (d, *J* = 3.3 Hz, 1H), 1.97−1.92 (m, 2H), 1.64−1.52 (m, 8H), 1.22 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 90.1, 75.2, 46.4, 33.0, 25.3, 22.7, 22.1; HRMS (ESI) calcd for $C_{11}H_{19}O$ $(M + H)^+$ *m/z* 167.1436, found 167.1424.



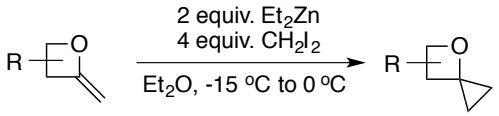
2p

3-Benzyl-2-methylenetetrahydrofuran (2p). 3-Benzyl-2-methylene-tetrahydrofuran (**2p**) was prepared from 3-benzyltetrahydrofuran-2-one (**8p**) (0.5 g, 2.8 mmol) using 1.5 equiv. of dimethyltitanocene. Purification by flash chromatography on silica gel (petroleum ether/EtOAc/Et_3N, 96.5:3:0.5) afforded 3-benzyl-2-methylene-tetrahydrofuran (**2p**) as a pale yellow oil (0.41 g, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 4.34 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.10 (ddd, *J* = 8.2, 8.2, 4.2 Hz, 1H), 3.96 (ddd, *J* = 8.2, 8.2, 6.5 Hz, 1H), 3.89 (dd,

J = 1.6, 1.6 Hz, 1H), 3.07 (dd, J = 13.5, 5.2 Hz, 1H), 3.03−2.95 (m, 1H), 2.63 (dd, J = 13.4, 9.6 Hz, 1H), 2.02−1.94 (m, 1H), 1.78−1.69 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.1, 140.0, 128.9, 128.4, 126.3, 78.9, 68.6, 42.6, 39.5, 31.1; HRMS (ESI) calcd for $C_{12}H_{15}O$ $(M + H)^+$ *m/z* 175.1123, found 175.1137.

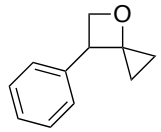
1.5.4 Preparation of 4-oxaspiro[2.3]hexanes (spirocyclopropyloxetanes)

[43]General procedure for the preparation of 4-oxaspiro[2.3]hexanes



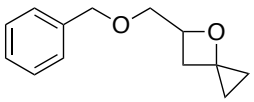
2a-o **4a-o**

A flame-dried three-neck reaction flask with a stir bar was charged with dry Et_2O (3/4 total volume) under N_2. After the solution was cooled to −15 °C neat Et_2Zn (2.0 equiv) was added drop-wise. The cloudy solution was stirred until clear (approx. 5 min), and CH_2I_2 (4.0 equiv) was then added while maintaining the internal temperature below −15 °C. After the addition was complete, the reaction was allowed to warm to −5 °C (over 10 min). The solution was cooled to −15 °C again, and a solution of 2-methyleneoxetane (1 equiv, 1.0 to 1.5 M) in dry Et_2O (1/4 total volume) was then added. The solution was stirred at −15 °C for 5 min and was then transferred to an ice-bath (0 °C). The reaction was stirred at 0 °C until complete consumption of 2-methyleneoxetane was observed by TLC (3-4 h). The reaction was quenched with saturated aqueous NH_4Cl (5 mL) by drop-wise addition at 0 °C with stirring for 5 min. The aqueous and organic layers were then separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*.



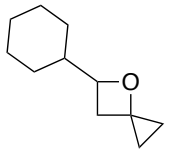
4a

6-Phenyl-4-oxaspiro[2.3]hexane (4a). 6-Phenyl-4-oxaspiro[2.3]hexane (**4a**) was prepared from 2-methylene-3-phenyloxetane (**2a**) (0.36 g, 2.5 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc 98:2) afforded 6-phenyl-4-oxaspiro[2.3]hexane (**4a**) as a colorless oil (0.33, 83%):[43] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.43 (m, 5H), 5.02 (dd, *J* = 8.3, 5.7 Hz, 1H), 4.66 (dd, *J* = 6.4, 5.7 Hz, 1H), 4.28 (dd, *J* = 8.3, 6.4 Hz, 1H), 0.97 (ddd, *J* = 10.9, 7.6, 6.5 Hz, 1H), 0.76 (ddd, *J* = 10.2, 7.4, 6.8, Hz, 1H), 0.62 (ddd, *J* = 10.8, 7.5, 6.5 Hz, 1H), 0.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 128.9, 128.4, 127.6, 75.4, 74.9, 46.5, 11.8, 9.3.



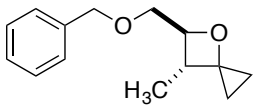
4c

5-Benzyloxymethyl-4-oxaspiro[2.3]hexane (4c). 5-Benzyloxymethyl-4-oxaspiro[2.3]-hexane (**4c**) was prepared using 4-benzyloxymethyl-2-methyleneoxetane (**2c**) (0.14 g, 0.75 mmol). Purification by flash chromatography on silica gel (petroleum ether/Et_2O, 94:6) afforded 5-benzyloxymethyl-4-oxaspiro[2.3]hexane (**4c**) as a colorless oil (0.12 g, 78%):[44b] IR (neat) 2922, 1558, 1457, 1103 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.94 (m, 1H), 4.68 (d, *J* = 12.1 Hz, 1H), 4.65 (d, *J* = 12.1 Hz, 1H), 3.80 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.71 (dd, *J* = 10.9, 3.8 Hz, 1H), 2.88 (dd, *J* = 10.8, 7.9 Hz, 1H), 2.70 (dd, *J* = 10.8, 6.2 Hz, 1H), 0.84 (m, 2H), 0.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.6, 127.9, 127.8, 75.8, 73.7, 73.6, 66.2, 31.3, 10.6, 10.5; HRMS (ESI) calcd for $C_{13}H_{16}O$ $(M + Na)^+$ *m/z* 227.1043, found 227.1066.



4e

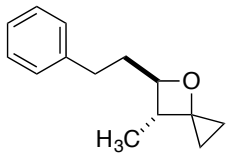
5-Cyclohexyl-4-oxaspiro[2.3]hexane (4e). 5-Cyclohexyl-4-oxaspiro[2.3]hexane (**4e**) was prepared using 4-cyclohexyl-2-methyleneoxetane (**2e**) (0.27 g, 1.8 mmol). Purification by flash chromatography on silica gel (petroleum ether/Et_2O, 99:1) afforded 5-cyclohexyl-4-oxaspiro[2.3]hexane (**4e**) as a pale yellow oil (0.12 g, 40%): IR (neat) 1966, 1925, 1738, 1570, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.42 (ddd, *J* = 7.2, 7.2, 7.2 Hz, 1H), 2.75 (dd, *J* = 10.7, 7.6 Hz, 1H), 2.54 (dd, *J* = 11.2, 6.4 Hz, 1H), 1.90 (m, 1H), 1.78−1.74 (m, 2H), 1.70−1.61 (m, 4H), 1.32−1.14 (m, 2H), 0.98 (m, 2H), 0.83−0.70 (m, 2H), 0.53 (ddd, *J* = 11.8, 5.9, 5.9 Hz, 1H), 0.43 (ddd, *J* = 10.4, 5.4, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.2, 65.2, 44.3, 32.6, 27.9, 26.7, 26.6, 25.9, 25.7, 10.7, 10.6.; HRMS (ESI) calcd for $C_{11}H_{19}O$ $(M + H)^+$ *m/z* 167.1436, found 167.1417.



4h

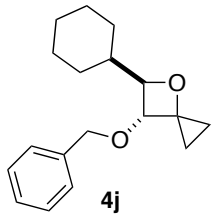
***trans*-5-Benzyloxymethyl-6-methyl-4-oxaspiro[2.3]hexane (4h).** *trans*-5-Benzyloxymethyl-6-methyl-4-oxaspiro[2.3]hexane (**4h**) was prepared using *trans*-4-benzyloxy-methyl-3-methyl-2-methylene-oxetane (**2h**) (0.57 g, 2.8 mmol). Purification by flash chromatography on slica gel (petroleum ether/EtOAc 95:5) afforded *trans*-5-benzyloxymethyl-6-methyl-4-oxaspiro[2.3]hexane (**4h**) as a colorless oil (0.49 g, 78%): IR (neat) 3065, 3031, 2961, 2926, 2871, 1722, 1455, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.28 (m, 4H), 7.25−7.20 (m, 1H), 4.61 (d, *J* = 12.4 Hz, 1H), 4.57 (d, *J* = 12.2 Hz, 1H), 4.46 (ddd, *J* = 5.7, 5.7, 3.9 Hz, 1H), 3.72 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.64 (dd, *J* = 10.9, 3.8 Hz, 1H), 2.90 (dq, *J* = 6.7, 6.7 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.81 (m, 1H), 0.58 (m, 2H), 0.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.4, 127.7, 127.7, 83.8, 73.5, 72.9, 71.3, 36.4, 15.6, 9.9, 6.5; HRMS (ESI) calcd

for $C_{14}H_{19}O_2$ $(M + H)^+$ *m/z* 219.1385, found 219.1388.



4i

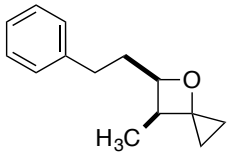
***trans*-6-Methyl-5-(2-phenylethyl)-4-oxaspiro[2.3]hexane (4i).** *trans*-6-Methyl-5-(2-phenylethyl)-4-oxaspiro[2.3]hexane (**4i**) was prepared using *trans*-3-methyl-2-methylene-4-(2-phenylethyl)oxetane (**2i**) (0.34 g, 1.8 mmol). Flash chromatography on silica gel (petroleum ether/Et_2O, 97:3) afforded *trans*-6-methyl-5-(2-phenylethyl)-4-oxaspiro[2.3]hexane (**4i**) as a colorless oil (0.28 g, 78%): IR (neat) 3027, 2927, 1604, 1454, 1194, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.17 (m, 5H), 4.35 (ddd, *J* = 7.2, 5.8, 5.8 Hz, 1H), 2.80−2.72 (m, 2H), 2.69−2.61 (m, 1H), 2.23−2.13 (m, 1H), 2.11−2.01 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.84 (ddd, *J* = 11.8, 7.5, 6.5 Hz, 1H), 0.66−0.56 (m, 2H), 0.44 (ddd, *J* = 10.6, 7.7, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 128.6, 126.0, 84.9, 70.4, 39.8, 38.6, 30.9, 15.7, 10.0, 6.5; HRMS (ESI) calcd for $C_{14}H_{19}O$ $(M + H)^+$ *m/z* 203.1436, found 203.1419.



4j

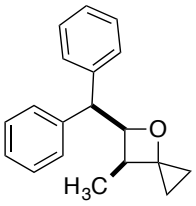
***trans*-6-Benzyloxy-5-cyclohexyl-4-oxaspiro[2.3]hexane (4j).** *trans*-6-Benzyloxy-5-cyclohexyl-4-oxaspiro[2.3]hexane (**4j**) using *trans*-3-benzyloxy-4-cyclohexyl-2-methyl-eneoxetane (**2j**) (0.19 g, 0.75 mmol). Purification by flash chromatography on silica gel (petroleum ether/Et_2O, 99:1) afforded *trans*-6-benzyloxy-5-cyclohexyl-4-oxaspiro-[2.3]hexane (**4j**) as pale yellow oil (0.12 g, 60%): IR (neat) 3067, 3034, 2865, 1729, 1451, 1274, 1112, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.39 (d, *J* = 2.9 Hz, 1H), 4.36 (dd, *J* = 3.8, 3.8 Hz, 1H), 4.33 (d, *J* = 4.6 Hz, 1H), 1.87 (m, 1H), 1.80−1.67 (m, 4H),

1.65−1.58 (m, 1H), 1.31−1.13 (m, 3H), 1.03 (dd, *J* = 11.8, 3.6 Hz, 1H), 0.97 (dd, *J* = 11.8, 3.4 Hz, 1H), 0.87 (m, 2H), 0.74 (m, 1H), 0.50-0.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 128.6, 128.0, 127.8, 89.9, 79.8, 71.5, 70.6, 42.0, 28.3, 27.2, 26.5, 25.9, 25.7, 9.8, 6.9; HRMS (ESI) calcd for $C_{18}H_{25}O_2$ $(M + H)^+$ *m/z* 273.1855, found 273.1784.



4k

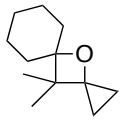
***cis*-6-Methyl-5-(2-phenylethyl)-4-oxaspiro[2.3]hexane (4k).** *cis*-6-Methyl-5-(2-phenylethyl)-4-oxaspiro[2.3]hexane (**4k**) was prepared using *cis*-3-methyl-2-methylene-4-(2-phenylethyl)oxetane (**2k**) (0.50 g, 2.6 mmol). Purification by flash chromatography on silica gel (petroleum ether/Et_2O, 97:3) afforded *cis*-6-methyl-5-(2-phenylethyl)-4-oxaspiro-[2.3]hexane (**4k**) as a colorless oil (0.41 g, 76%): IR (neat) 3078, 3063, 2933, 2238, 1641, 1497, 1173, 798 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.21 (m, 5H), 4.83 (ddd, *J* = 9.7, 8.3, 4.5 Hz, 1H), 3.17 (dq, *J* = 7.1, 7.1 Hz, 1H), 2.78 (ddd, *J* = 13.9, 10.0, 5.1 Hz, 1H), 2.58 (ddd, *J* = 13.9, 9.7, 6.6 Hz, 1H), 2.18 (dddd, *J* = 14.2, 9.9, 9.9, 5.4 Hz, 1H), 1.89 (dddd, *J* = 10.6, 10.6, 6.6, 4.2 Hz, 1H) 1.04 (d, *J* = 7.0 Hz, 3H), 0.89−0.83 (m, 1H), 0.63−0.58 (m, 1H), 0.56−0.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 128.6, 128.5, 126.0, 80.1, 71.2, 36.1, 33.7, 31.4, 11.1, 9.7, 6.7; HRMS (ESI) calcd for $C_{14}H_{19}O$ $(M + H)^+$ *m/z* 203.1436, found 203.1418.



4l

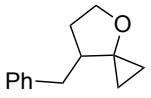
***cis*-5-Benzhydryl-6-methyl-4-oxaspiro[2.3]hexane (4l).** *cis*-5-Benzhydryl-6-methyl-4-oxaspiro[2.3]hexane (**4l**) was prepared using *cis*-4-benzhydryl-3-methyl-2-methylene-oxetane (**2l**) (0.12 g, 0.48 mmol). Purification by flash chromatography on silica gel (petroleum

ether/Et_2O, 96:4) afforded *cis*-5-benzhydryl-6-methyl-4-oxaspiro[2.3]hexane (**4l**) as a colorless oil (0.11 g, 86%): IR (neat) 3082, 2925, 1495, 1451, 970, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.13 (m, 10H), 5.63 (dd, *J* = 11.0, 7.4 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 3.20 (dq, *J* = 7.2, 7.2 Hz, 1H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.92-0.87 (m, 1H), 0.67−0.62 (m, 1H) 0.60−0.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.5, 128.9, 128.7, 128.5, 128.3, 126.8, 126.7, 81.8, 70.9, 52.7, 37.0, 12.0, 10.0, 6.4; HRMS (ESI) calcd for $C_{19}H_{21}O$ $(M + H)^+$ *m/z*, 265.1592, found 265.1599.



4n

9,9-Dimethyl-3-oxadispiro[2.2.5.0]undecane (4n). 9,9-Dimethyl-3-oxadispiro[2.2.5.0]undecane (**4n**) was prepared using 3,3-dimethyl-2-methylene-1-oxaspiro[3.5]nonane (**2n**) (0.70 g, 4.2 mmol). Flash chromatography on silica gel (petroleum ether/Et_2O, 99.5:0.5) afforded 9,9-dimethyl-3-oxadispiro[2.2.5.0]undecane (**4n**) as a colorless oil (0.56 g, 75%): ^1H NMR (400 MHz, $CDCl_3$) δ 2.00 (m, 2H), 1.59−1.50 (br m, 8H), 1.05 (s, 6H), 0.58 (m, 2H), 0.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.9, 72.9, 41.3, 33.8, 25.6, 22.7, 20.7, 7.0; HRMS (ESI) calcd for $C_{12}H_{21}O$ $(M + H)^+$ *m/z* 181.1592, found 181.1587.



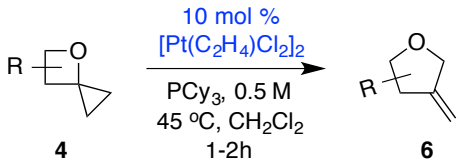
4p

7-Benzyl-4-oxaspiro[2.4]heptane (4p). 7-Benzyl-4-oxaspiro[2.4]heptane (**4p**) was prepared using 3-benzyl-2-methylenetetrahydrofuran (**2p**) (420 mg, 2.4 mmol). Purification by flash chromatography on silica gel (petroleum ether/Et_2O, 98:2) afforded 7-benzyl-4-oxaspiro[2.4]heptane (**4p**) as a colorless oil (434 g, 96%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.19 (m, 5H), 3.96 (ddd, *J* = 8.2, 8.2, 5.3 Hz, 1H), 3.84 (ddd, *J* = 8.0, 8.0, 8.0 Hz, 1H), 2.69 (dd, *J* = 13.5, 5.0 Hz, 1H), 2.52 (dd, *J* = 13.4, 10.3 Hz, 1H), 2.42−2.35 (m, 1H), 2.16−2.08 (m, 1H), 1.85−1.77 (m, 1H), 0.87−0.76 (m, 2H), 0.70−0.65 (m, 1H), 0.48−0.43 (m, 1H); ^{13}C

NMR (400 MHz, $CDCl_3$) δ 140.7, 128.9, 128.5, 126.1, 67.2, 66.3, 43.3, 38.3, 32.2, 10.0, 7.0; HRMS (ESI) calcd for $C_{13}H_{17}O$ $(M + H)^+$ *m/z*, 189.1279, obs. 189.1298.

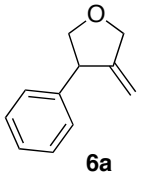
1.5.5 Pt(II)-catalyzed expansion of 4-oxaspiro[2.3]hexanes

General procedure for the Pt(II)-catalyzed expansion of 4-oxaspiro[2.3]hexanes



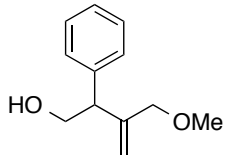
4 **6**

Zeise's dimer (0.1 equiv) and PCy_3 (0.2 equiv) were mixed in dry CH_2Cl_2 (1/4 of total volume) in a nitrogen purged flask/NMR reaction tube at rt. 4-Oxaspiro[2.3]hexane (1 equiv, 0.5 M) dissolved in dry CH_2Cl_2 (3/4 of total volume) was added and the reaction mixture was heated at 45 °C. The reaction was monitored by NMR/TLC for disappearance of the 4-oxaspiro[2.3]hexane. The reaction mixture was concentrated *in vacuo*, and the resulting oil was purified by flash column chromatography on neutral alumina or silica gel.



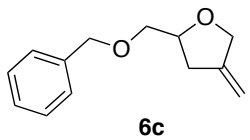
6a

3-Methylene-4-phenyltetrahydrofuran (6a). The general procedure was followed using 6-phenyl-4-oxaspiro[2.3]hexane (**4a**) (0.10 g, 0.63 mmol). The reaction was stirred for 3.5 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc, 96:4) afforded 3-methylene-4-phenyltetrahydrofuran (**6a**) as a colorless oil (34 mg, 34%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.24 (m, 3H), 5.05 (m, 1H), 4.77 (dd, *J* = 4.6, 2.2 Hz, 1H), 4.51 (m, 2H), 4.29 (dd, *J* = 6.2, 6.2 Hz, 1H), 3.85 (m, 1H), 3.81 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 141.3, 128.8, 128.5, 127.0, 106.2, 76.2, 72.3, 50.8. HRMS (ESI) calcd for $C_{11}H_{11}O$ $(M - H)^+$ *m/z* 159.0810, found 159.0795.



7a

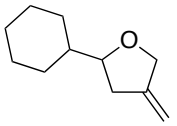
3-Methoxymethyl-2-phenylbut-3-en-1-ol (7a). The general procedure was followed using 6-phenyl-4-oxaspiro[2.3]hexane (**4a**) (60 mg, 0.37 mmol) in the presence of MeOH (20 equiv). The reaction was stirred for 2 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc, 95:5) afforded 3-methoxymethyl-2-phenylbut-3-en-1-ol (**7a**) as a yellow oil (44 mg, 50%): IR (neat) 3060, 2924, 2853, 1715, 1453, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 5.30 (s, 1H), 5.15 (s, 1H), 4.02 (dd, *J* = 18.1, 10.7 Hz, 1H), 3.91 (dd, *J* = 17.6, 6.8 Hz, 1H), 3.77 (d, *J* = 12.8 Hz, 1H), 3.75 (d, *J* = 12.6 Hz, 1H), 3.61 (dd, *J* = 7.0, 7.0 Hz, 1H), 3.27 (s, 3H), 2.01 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 140.2, 128.8, 128.4, 127.2, 114.2, 75.2, 65.2, 58.2, 51.3; HRMS (FAB) calcd for $C_{12}H_{17}O_2$ $(M + H)^+$ *m/z* 193.1229, found 193.1236.



6c

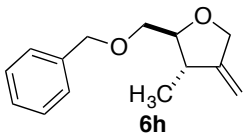
2-Benzyloxymethyl-4-methylenetetrahydrofuran (6c). The general procedure was followed using 5-benzyloxymethyl-4-oxaspiro[2.3]hexane (**4c**) (39 mg, 0.19 mmol). The reaction mixture was stirred for 40 min. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc 96:4) afforded 2-benzyloxymethyl-4-methylenetetrahydrofuran (**6c**) as a colorless oil (25 mg, 65%):[65] IR (neat) 2919, 2857, 1497, 1101, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.96 (ddd, *J* = 4.4, 2.2, 2.2 Hz, 1H), 4.90 (ddd, *J* = 4.3, 2.1, 2.1 Hz, 1H), 4.59 (d, *J* = 12.1 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 1H), 4.39 (m, 1H), 4.26 (m, 1H), 4.19 (m, 1H), 3.15 (m, 2H), 2.58 (m, 1H), 2.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 147.5, 138.2, 128.4, 127.7, 127.6, 104.4, 78.5, 73.4, 72.0, 71.2, 35.2; HRMS (ESI) calcd for $C_{13}H_{15}O_2$ $(M - H)^+$ *m/z* 203.1072, found 203.1046.



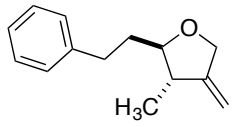
6e

2-Cyclohexyl-4-methylenetetrahydrofuran (6e). The general procedure was followed using 5-cyclohexyl-4-oxaspiro[2.3]hexane (**4e**) (35 mg, 0.21 mmol). The reaction was stirred for 1.5 h. Purification by column chromatography on neutral alumina (petroleum ether/Et_2O, 99:1) afforded 2-cyclohexyl-4-methylenetetrahydrofuran (**6e**) as a colorless oil (21 mg, 62%):[66] ^1H NMR (400 MHz, $CDCl_3$) δ 4.95 (dd, *J* = 2.2, 2.2 Hz, 1H), 4.87 (dd, *J* = 2.2, 2.2 Hz, 1H), 4.36 (m, 1H), 4.21 (m, 1H), 3.60 (m, 1H), 2.56 (m, 1H), 2.25 (m, 1H), 1.96 (m, 2H), 1.80−1.59 (m, 4H), 1.44−1.14 (m, 3H), 0.99 (m, 2H). Spectral data are in accordance with literature reference 65.



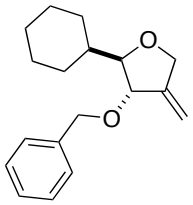
6h

***trans*-2-Benzyloxymethyl-3-methyl-4-methylenetetrahydrofuran** (**6h**). The general procedure was followed using *trans*-5-(benzyloxymethyl)-6-methyl-4-oxaspiro[2.3]-hexane (**4h**) (50 mg, 0.23 mmol). The reaction mixture was stirred for 45 min. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc, 96:4) afforded *trans*-2-benzyloxymethyl-3-methyl-4-methylenetetrahydrofuran (**6h**) as a colorless oil (34.5 mg, 69%): IR (neat) 3064, 2964, 2931, 2872, 1766, 1723, 1453, 1379, 1091, 913 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 4.92 (m, 1H), 4.88 (ddd, *J* = 2.5, 2.5, 2.5 Hz, 1H), 4.60 (s, 2H), 4.52−4.48 (m, 1H), 4.35−4.30 (m, 1H), 3.67−3.54 (m, 3H), 2.46 (m, 1H), 1.09 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 138.4, 128.6, 127.9, 127.8, 103.3, 85.4, 73.7, 71.3, 40.1, 15.1; HRMS (ESI) calcd for $C_{14}H_{17}O_2$ $(M + H)^+$ *m/z* 217.1229, found 217.1198.



6i

***trans*-3-Methyl-4-methylene-2-(2-phenylethyl)tetrahydrofuran (6i).** The general procedure was followed using *trans*-4-methyl-5-(2-phenylethyl)-4-oxaspiro[2.3]hexane (**4i**) (50 mg, 0.25 mmol). The reaction mixture was stirred for 45 min. Purification by column chromatography on neutral alumina (petroleum ether/Et_2O, 98:2) afforded *trans*-3-methyl-4-methylene-2-(2-phenylethyl)tetrahydrofuran (**6i**) as a colorless oil (40 mg, 80%): IR (neat) 3027, 2917, 2853, 1765, 1496, 1455, 1377, 1030, 909 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23−7.10 (m, 5H), 4.84 (m, 1H), 4.79 (m, 1H), 4.42 (m, 1H), 4.23 (m, 1H), 3.32 (ddd, *J* = 8.8, 8.8, 3.1 Hz, 1H), 2.82 (ddd, *J* = 13.9, 10.8, 5.1 Hz, 1H), 2.62 (ddd, *J* = 13.8, 10.3, 6.4 Hz, 1H), 2.2 (m, 1H), 1.88 (m, 1H), 1.77 (m, 1H), 1.0 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 142.5, 128.6, 128.6, 126.0, 102.9, 85.8, 70.9, 43.7, 36.0, 32.7, 14.9; HRMS (ESI): calcd for $C_{14}H_{19}O$ $(M - H)^+$ *m/z* 201.1279, found: 201.1278.



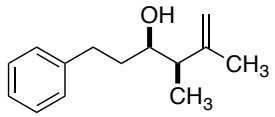
6j

***trans*-3-Benzyloxy-2-cyclohexyl-4-methylenetetrahydrofuran (6j).** The general procedure was followed using *trans*-6-benzyloxy-5-cyclohexyl-4-oxaspiro[2.3]hexane (**4j**) (60 mg, 0.22 mmol). The reaction mixture was stirred for 2 h. Purification by column chromatography on neutral alumina (petroleum ether/Et_2O, 95:5) afforded *trans*-3-benzyloxy-2-cyclohexyl-4-methylenetetrahydrofuran (**6j**) as a colorless oil (45 mg, 75%): IR (neat) 2925, 2853, 1731, 1573, 1451, 1260, 1065 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.34 (m, 4H), 7.30−7.27 (m, 1H), 5.24 (m, 1H), 5.19 (m, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.46−4.43

(m, 1H), 4.32−4.27 (m, 1H), 4.09 (m, 1H), 3.76 (dd, *J* = 7.4, 3.0 Hz, 1H), 1.82 (m, 1H), 1.74−1.72 (m, 2H), 1.65−1.61 (m, 2H), 1.39−1.32 (m, 1H), 1.25−1.13 (m, 3H), 1.10−0.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 138.4, 128.6, 128.0, 127.8, 109.8, 88.6, 81.9, 70.2, 70.0, 40.6, 29.6, 28.8, 26.6, 26.3, 26.1; HRMS (ESI): calcd for $C_{18}H_{25}O_2$ $(M + H)^+$ *m/z* 273.1855, found 273.1837.

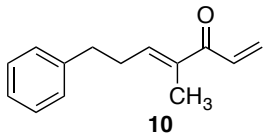
Reaction of *cis*-6-methyl-5-(2-phenylethyl)-4-oxaspiro[2.3]hexane (4k).

The general procedure was followed using *cis*-6-methyl-5-(2-phenylethyl)-4-oxaspiro[2.3]hexane (**4k**) (110 mg, 0.54 mmol). The reaction mixture was stirred for 16 h. The reaction was monitored by NMR/TLC for disappearance of *cis*-6-methyl-5-2-phenylethyl-4-oxaspiro[2.3]hexane. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc 99.5:0.5 to 95:5) afforded (*3*R*,*4*R*)-2,3-dimethyl-6-phenylhex-1-ene-4-ol (**12**) and (*E*)-4-methyl-6-phenylhepta-1,4-diene-3-one (**13**) as the major and minor products, respectively. *cis*-3-Methyl-4-methylene-2-(2-phenylethyl)tetrahydrofuran (**6k**) was also observed and obtained in a trace amount with an unknown impurity.



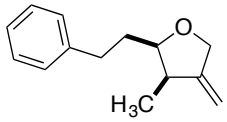
9

(3*R,4*R**)-2,3-Dimethyl-6-phenylhex-1-ene-4-ol** (**9**) was obtained as the major product in the above reaction as a clear oil (46 mg, 42%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.26 (m, 2H), 7.22−7.16 (m, 3H), 4.85 (s, 1H), 4.78 (s, 1H), 3.59 (m, 1H), 2.85 (ddd, *J* = 14.0, 9.3, 6.0 Hz, 1H), 2.66 (ddd, *J* = 16.4, 9.0, 7.0 Hz, 1H), 2.20 (dq, *J* = 6.8, 6.8 Hz, 1H), 1.76 (m, 2H), 1.69 (s, 3H), 1.06 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 142.4, 128.6, 128.6, 126.0, 111.7, 72.0, 46.6, 36.7, 32.8, 21.4, 13.6; HRMS (ESI) calcd for $C_{14}H_{21}O$ $(M + H)^+$ *m/z* 205.1592, found 205.1583.



10

(*E*)-4-Methyl-7-phenylhepta-1,4-diene-3-one (**10**) was obtained as the minor product from the above reaction as colorless oil (21 mg, 20%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.28 (m, 2H), 7.22−7.18 (m, 3H), 6.87 (dd, *J* = 17.0, 10.6 Hz, 1H), 6.65 (m, 1H), 6.19 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.68 (dd, *J* = 10.6, 1.8 Hz, 1H), 2.79 (dd, *J* = 7.4, 7.4 Hz, 1H), 2.59 (ddd, *J* = 7.4, 7.4, 7.4 Hz, 1H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 142.7, 141.2, 138.3, 132.1, 128.7, 128.5, 128.1, 126.4, 34.9, 31.1, 11.8; HRMS (ESI): calcd for $C_{14}H_{17}O$ (M + H^+) *m/z* 201.1279, found 201.1249.



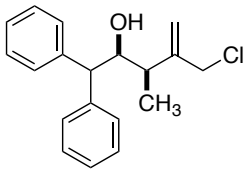
6k

***cis*-3-Methyl-4-methylene-2-(2-phenylethyl)tetrahydrofuran** (**6k**) was also observed and obtained as a colorless oil in a trace amount with an unknown impurity: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.16 (m, 5H), 4.89 (m, 1H), 4.84 (m, 1H), 4.41 (d, *J* = 13.3 Hz, 1H), 4.30 (d, *J* = 14.0 Hz, 1H), 3.95 (ddd, *J* = 8.9, 6.0, 4.6 Hz, 1H), 2.85 (m, 2H), 2.69 (m, 2H), 1.01 (d, *J* = 7.1 Hz, 3H).

Reaction of *cis*-5-benzhydryl-6-methyl-4-oxaspiro[2.3]hexane (4l).

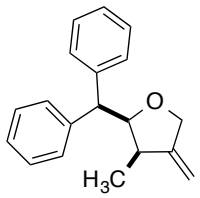
The general procedure was followed using *cis*-5-benzhydryl-6-methyl-4-oxaspiro[2.3]hexane (**4l**) (27 mg, 0.10 mmol). The reaction mixture was stirred for 21 h. The reaction was monitored by NMR/TLC for disappearance of *cis*-5-benzhydryl-6-methyl-4-oxaspiro[2.3]hexane. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc 99:1 to 95:5) afforded (2S*,3*R**)-4-chloromethyl-3-methyl-1,1-diphenylpent-4-ene-2-ol (**8**) as the major product and *cis*-5-benzhydryl-4-methyl-3-methylenetetrahydrofuran (**6l**) as the minor

product.



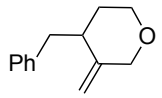
8

(2S*,3*R)-4-Chloromethyl-3-methyl-1,1-diphenylpent-4-ene-2-ol** (**8**) was obtained as a clear oil (13 mg, 39%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.19 (m, 10H), 5.30 (s, 1H), 5.12 (s, 1H), 4.53 (ddd, *J* = 9.4, 3.1, 3.1 Hz, 1H), 4.14 (d, *J* = 3.1 Hz, 1H), 4.04 (d, *J* = 11.8 Hz, 1H), 4.04 (d, *J* = 9.5 Hz, 1H), 2.51 (m, 3H), 1.56 (d, *J* = 3.1 Hz, 1H), 1.13 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 142.1, 141.9, 129.1, 128.8, 128.4, 127.1 127.0, 116.2, 74.5, 56.1, 47.9, 38.8, 12.0; HRMS (ESI) calcd for $C_{19}H_{25}NClO$ $(M + NH_4)^+$ *m/z* 318.1625, found 318.1632.



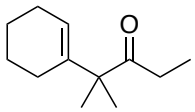
6l

***cis*-2-Benzhydryl-3-methyl-4-methylenetetrahydrofuran** (**6l**) was obtained from the reaction of *cis*-5-benzhydryl-6-methyl-4-oxaspiro[2.3]hexane (**4l**) in a trace amount as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.14 (m, 10H), 4.91 (m, 1H), 4.84 (m, 1H), 4.68 (dd, *J* = 10.9, 4.7 Hz, 1H), 4.48 (m, 1H), 4.23 (m, 1H), 4.03 (d, *J* = 10.9 Hz, 1H), 2.66 (m, 1H), 0.98 (d, *J* = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 143.4, 142.3, 128.9, 128.7, 128.3, 128.1, 126.8, 126.6, 103.7, 84.3, 70.7, 52.6, 41.5, 15.5; HRMS (ESI) calcd for $C_{19}H_{21}O$ $(M + H)^+$ *m/z* 263.1436, found 263.1439.



6p

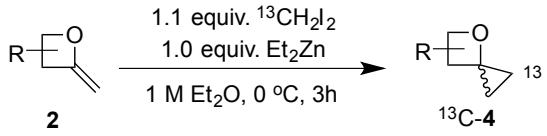
4-Benzyl-3-methylenetetrahydropyran (6p). The general procedure was followed using 4-7-benzyl-4-oxaspiro[2.4]heptane (**4p**) (50 mg, 0.26 mmol). The reaction mixture was stirred for 24 h. Purification by column chromatography on neutral alumina (petroleum ether/Et_2O, 98:2) afforded 4-benzyl-3-methylenetetrahydropyran (**6p**) as a colorless oil (10 mg, 20%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.16 (m, 5H), 4.92 (s, 1H), 4.85 (s, 1H), 4.20 (d, J = 11.9 Hz, 1H), 3.93 (d, J = 11.9 Hz, 1H), 3.94-3.90 (m, 2H), 3.54-3.49 (m, 1H), 3.10 (dd, J = 12.8, 4.4 Hz, 1H), 2.58-2.52 (m, 1H), 1.65-1.61 (m, 1H), 1.44-1.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 140.3, 129.3, 128.5, 126.2, 108.6, 73.2, 67.6, 41.7, 38.5, 33.5; HRMS (ESI): calcd for $C_{13}H_{15}O$ $(M - H)^+$ *m/z* 187.1123, found: 187.1132.



13

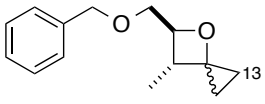
2-(1-Cyclohexenyl)-2-methylpentan-3-one (13). The general procedure for the reaction of 4-oxaspirohexane with Zeise's dimer was followed using 9,9-dimethyl-3-oxadispiro[2.2.5.0]undecane (**4n**) (20 mg, 0.11 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc, 99:1) afforded 2-(1-cyclohexenyl)-2-methylpentan-3-one (**13**) as clear oil (10 mg, 50%):[44a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (m, 1H), 2.35 (q, *J* = 7.3 Hz, 2H), 2.05 (m, 2H), 1.75 (m, 2H), 1.54 (m, 4H), 1.15 (s, 6H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6, 140.4, 122.1, 53.6, 29.7, 26.1, 25.7, 23.3, 23.3, 22.4, 8.7; HRMS (ESI) calcd for $(M + H)^+$ $C_{12}H_{21}O$ *m/z* 181.1592, found 181.1562.

1.5.6 Preparation of ^{13}C-labeled 4-oxaspiro[2.3]hexanes



2 ^{13}C-**4**

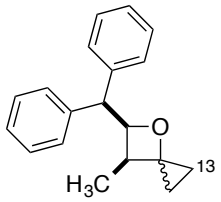
A flame-dried three-neck reaction flask with a stir bar was charged with dry Et_2O (3/4 total volume) under N_2. After the solution was cooled to −15 °C neat Et_2Zn (1.0 equiv) was added drop-wise. The cloudy solution was stirred until clear (approx. 5 min), and $^{13}CH_2I_2$ (1.1 equiv) was then added while maintaining the internal temperature below −15 °C. After the addition was complete, the reaction was allowed to warm to −5 °C (over 10 min). The solution was cooled to −15 °C again, and a solution of 2-methyleneoxetane (1 equiv) in dry Et_2O (1/4 total volume) was then added. The final solution is 1.0 M of methyleneoxetane in Et_2O. The solution was stirred at −15 °C for 5 min and was then transferred to an ice-bath (0 °C). The reaction was stirred at 0 °C until complete consumption of 2-methyleneoxetane was observed by TLC (3-4 h). The reaction was quenched with saturated aqueous NH_4Cl (5 mL) by drop-wise addition at 0 °C with stirring for 5 min. The aqueous and organic layers were then separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in *vacuo*.



^{13}C-**4h**

^{13}C-Labeled *trans*-5-benzyloxymethyl-6-methyl-4-oxaspiro[2.3]hexane (^{13}C-4h). The general procedure for the preparation of ^{13}C-labeled 4-oxaspiro[2.3]hexanes was followed using *trans*-4-benzyloxymethyl-3-methyl-2-methyleneoxetane (**2h**) (0.1 g, 0.5 mmol. Purification by column chromatography on silica gel (petroleum ether/EtOAc 95:5) afforded ^{13}C-labeled *trans*-5-benzyloxymethyl-6-methyl-4-oxaspiro[2.3]hexane (**^{13}C-4h**) as a mixture of

isotopomers (colorless oil) (0.08 g, 71%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.25 (m, 5H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.50 (ddd, *J* = 5.7, 5.7, 3.8 Hz, 1H), 3.76 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.76 (dd, *J* = 11.0, 3.8 Hz, 1H), 2.94 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.10−0.14 (m[1], 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.6, 127.8, 127.8, 83.9, 73.7, 73.0, 71.5 (71.3 for the other isotopomer), 36.5, 15.7, 10.0 (^{13}C-labeled), 6.6 (^{13}C-labeled); HRMS (ESI) calcd for $C_{13}{}^{13}CH_{17}O_2$ $(M + H)^+$ *m/z* 220.1385, found 220.1375.



^{13}C-**4l**

^{13}C-Labeled *cis*-5-benzhydryl-6-methyl-4-oxaspiro[2.3]hexane (^{13}C-4l). The general procedure for the preparation of ^{13}C labeled 4-oxaspiro[2.3]hexanes was followed using *cis*-4-benzhydryl-3-methyl-2-methyleneoxetane (**2l**) (120 mg, 0.48 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc 95:5) afforded ^{13}C labeled *cis*-5-benzhydryl-6-methyl-4-oxaspiro[2.3]hexane (^{13}C-**4l**) as a mixture of isotopomers (colorless oil) (69 mg, 55%): IR (neat) 3082, 2925, 1495, 1451, 970, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.11 (m, 10 H), 5.62 (dd, *J* = 11.1, 7.3 Hz, 1H), 4.46 (d, *J* = 11.1 Hz, 1H), 3.20 (m, 1H), 0.95 (d, *J* = 7.2 Hz, 3H), 1.26−0.53 (m[2], 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 141.5, 128.9, 128.7, 128.6, 128.3, 126.8, 126.7, 81.8, 71.0 (70.8 for the other isotopomer), 52.7, 37.0, 10.0 (^{13}C-labeled carbon), 6.4 (^{13}C-labeled carbon); HRMS (ESI) calcd for $C_{18}{}^{13}CH_{21}O$ $(M + H)^+$ *m/z* 266.1592, found 266.1605.

[1] Complex multiplets were observed as a result of $^{1}J_{^{13}C\text{-}H}$ and $^{2}J_{^{13}C\text{-}H}$ coupling.
[2] Complex multiplets were observed as a result of $^{1}J_{^{13}C\text{-}H}$ and $^{2}J_{^{13}C\text{-}H}$ coupling.

1.5.7 ^{13}C NMR monitoring for the reaction of ^{13}C-labeled oxaspirohexane with Zeise's dimer.

Zeise's dimer (0.5 equiv) and PCy_3 (1.0 equiv) were mixed in dry CD_2Cl_2 (0.3 mL) in a N_2 purged NMR reaction tube. 4-Oxaspiro[2.3]hexane (0.1 mmol) dissolved in dry CD_2Cl_2 (0.2 mL) was added at −30 °C. The solution was then allowed to warm to room temperature. The reaction was monitored by ^{13}C NMR until complete conversion of starting material to products.

^{13}C-Labeled *trans*-5-benzyloxymethyl-6-methyl-4-oxaspiro[2.3]hexane (^{13}C-4h)

Figure 9a. ^{13}C NMR Spectrum (CD_2Cl_2, rt, 100 MHz) of the reaction after **1 h**:

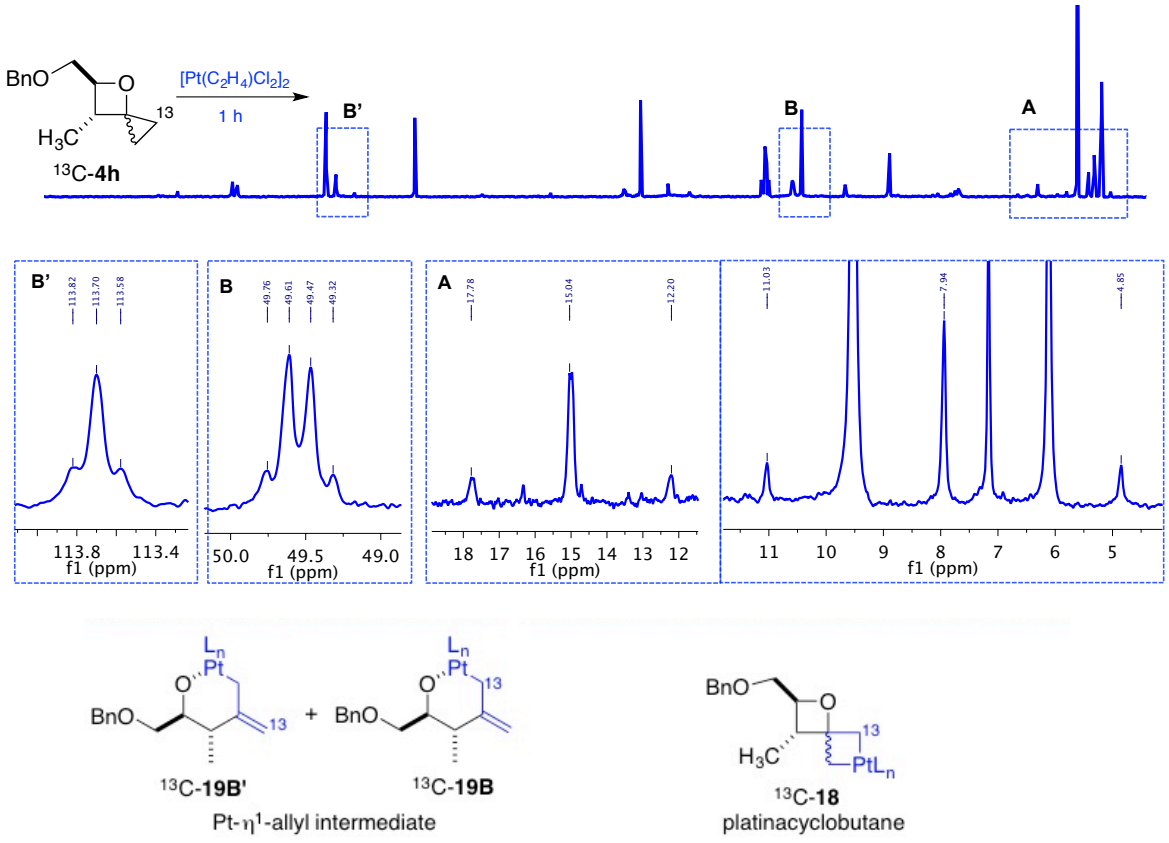


Figure 9b. ^{13}C-DEPT NMR Spectrum (CD_2Cl_2, rt, 100 MHz) of the reaction after **2 h**:

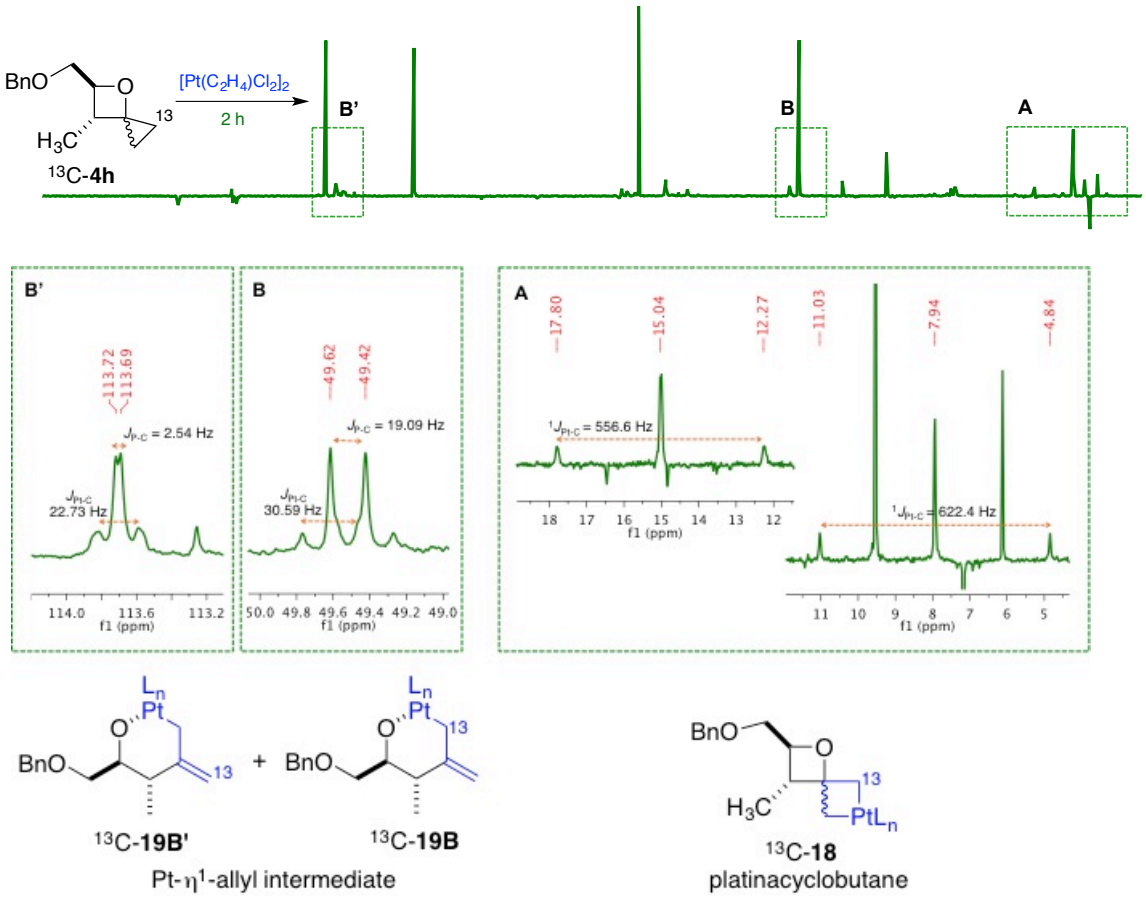
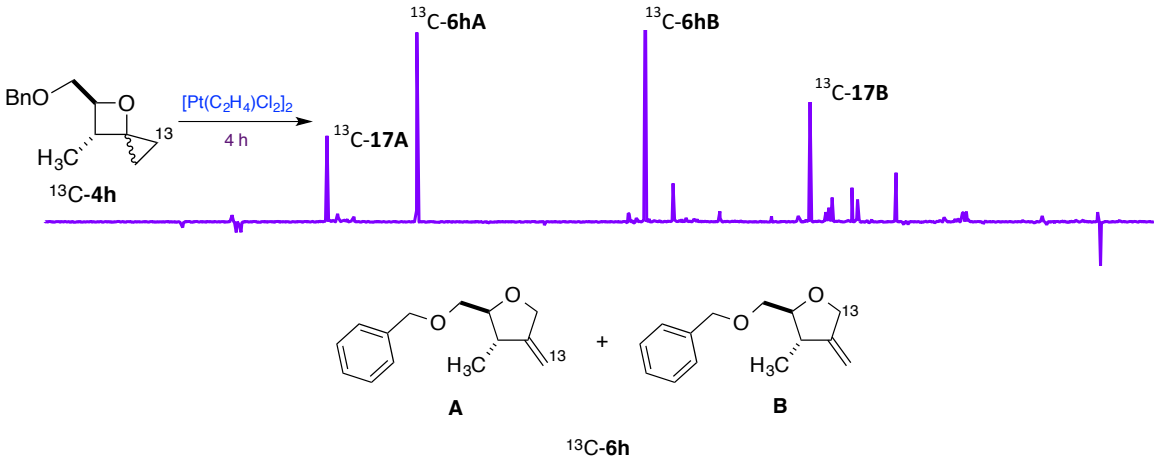
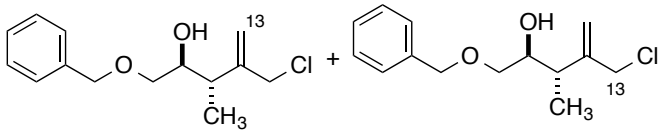


Figure 9c. ^{13}C-DEPT NMR Spectrum (CD_2Cl_2, rt, 100 MHz) of the reaction after **4 h**:

The labeled peaks correspond to the ^{13}C-labeled carbons in compounds ^{13}C-**6h** and ^{13}C-**7**, as major and minor products, respectively, and were both isolated.



^{13}C-labeled *trans*-5-benzyloxymethyl-4-methyl-3-methylenetetrahydrofuran (^{13}C-6h). The general procedure was followed using ^{13}C-labeled *trans*-5-benzyloxymethyl-6-methyl-4-oxaspiro[2.3]hexane (^{13}C-**4h**) (22 mg, 0.1 mmol). The reaction mixture was concentrated in *vacuo*. Purification by column chromatography using petroleum ether/Et_2O (95:5) afforded an isotopomeric mixture of ^{13}C-labeled *trans*-5-benzyloxymethyl-4-methyl-3-methylenetetrahydrofuran (^{13}C-**6h**) as a colorless oil (12 mg, 55%): ^{1}H NMR (400 MHz, $CDCl_3$) for isotopomer **A**: δ 7.35−7.25 (m, 5H), 4.96 (dm[3], $^1J^{13}_{C\text{-}H}$ = 156.9 Hz, 1H), 4.91 (dm[3], $^1J^{13}_{C\text{-}H}$ = 157.7 Hz, 1H), 4.63 (s, 2H), 4.53−4.49 (m, 1H), 4.39−4.31 (m, 1H), 3.70−3.57 (m, 3H), 2.49 (m, 1H), 1.12 (d, *J* = 6.7 Hz, 3H); for isotopomer **B**: δ 7.35−7.25 (m, 5H), 4.96 (m, 1H), 4.91 (m, 1H), 4.63 (s, 2H), 4.53−4.49 (dm[3], $^1J^{13}_{C\text{-}H}$ = 146.4 Hz, 1H), 4.35−4.30 (dm[3], $^1J^{13}_{C\text{-}H}$ = 143.0 Hz, 1H), 3.70−3.57 (m, 3H), 2.49 (m, 1H), 1.12 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 138.4, 128.6, 127.9, 127.8, 103.3 (^{13}C-labeled carbon in isotopomer **A**), 85.4, 73.7, 71.3, (^{13}C-labeled carbon in isotopomer **B**), 70.8, 40.0, 15.1 (match with compound **6h**); HRMS (ESI) calcd for $C_{13}{}^{13}CH_{19}O_2$ $(M + H)^+$ *m/z* 220.1385, found 220.1379; $(M + NH_4)^+$, calc. 237.1651, found 237.1629, $(M - OH)^+$, 202.1279, found 202.1298 and $(M - H)^+$, 218.1229, found 218.1224.



A **B**

^{13}C-**17**

^{13}C-labeled (2*R, 3*S**)-1-benzyloxy-4-chloromethyl-3-methyl-pent-4-ene-2-ol** (^{13}C-**17**) was obtained as the minor product (colorless oil, 5 mg, 20%): ^{1}H NMR (400 MHz, $CDCl_3$) for isotopomer **A**: δ 7.38−7.30 (m, 5H), 5.31 (d, $^1J^{13}_{C\text{-}H}$ = 157.8 Hz, 1H), 5.11 (d, $^1J^{13}_{C\text{-}H}$ = 156.8 Hz, 1H), 4.59 (d, *J* = 11.2 Hz), 4.54 (d, *J* = 11.9 Hz), 4.14 {dd, *J* = 5.9 Hz ($^3J^{13}_{C\text{-}H}$), 5.9 Hz, 2H}, 3.79 (m, 1H), 3.59 (dd, *J* = 9.6, 3.1 Hz, 1H), 3.43 (dd, *J* = 9.6, 7.2 Hz, 1H), 2.54 (m, 1H), 2.35 (d, *J*

[3] *dm* = *doublet of multiplet*; where the large coupling constant ($^1J^{13}_{C\text{-}H}$) is shown.

= 3.7 Hz, 1H), 1.09 (d, *J* = 7.1 Hz, 3H); for isotopomer **B**: δ 7.38−7.30 (m, 5H), 5.31 (d, $^{3}J^{13}_{C\text{-}H}$ = 8.0 Hz, 1H), 5.11 (d, $^{3}J^{13}_{C\text{-}H}$ = 13.6 Hz, 1H), 4.59 (d, *J* = 11.2 Hz), 4.54 (d, *J* = 11.9 Hz), 4.14 {dd, *J* = 151.0 Hz ($^{1}J^{13}_{C\text{-}H}$), 7.0 Hz, 2H}, 3.79 (m, 1H), 3.59 (dd, *J* = 9.6, 3.1 Hz, 1H), 3.43 (dd, *J* = 9.6, 7.2 Hz, 1H), 2.54 (m, 1H), 2.35 (d, *J* = 3.7 Hz, 1H), 1.09 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 138.1, 128.7, 128.1, 128.0, <u>115.9</u> (^{13}C-labeled carbon in isotopomer **A**), 77.4, 73.7, 72.6, 53.6, <u>48.3</u> (^{13}C-labeled carbon in isotopomer **B**), 16.9; HRMS (ESI) calcd for $C_{13}{}^{13}CH_{20}ClO_2$ $(M + H)^+$ *m/z* 256.1152, found 256.1168.

^{13}C-Labeled *cis*-5-benzhydryl-6-methyl-4-oxaspiro[2.3]hexane (^{13}C-4l)

Figure 10a. ^{13}C DEPT NMR (CD_2Cl_2, room temp., 100 MHz) of the reaction after **1 h**:

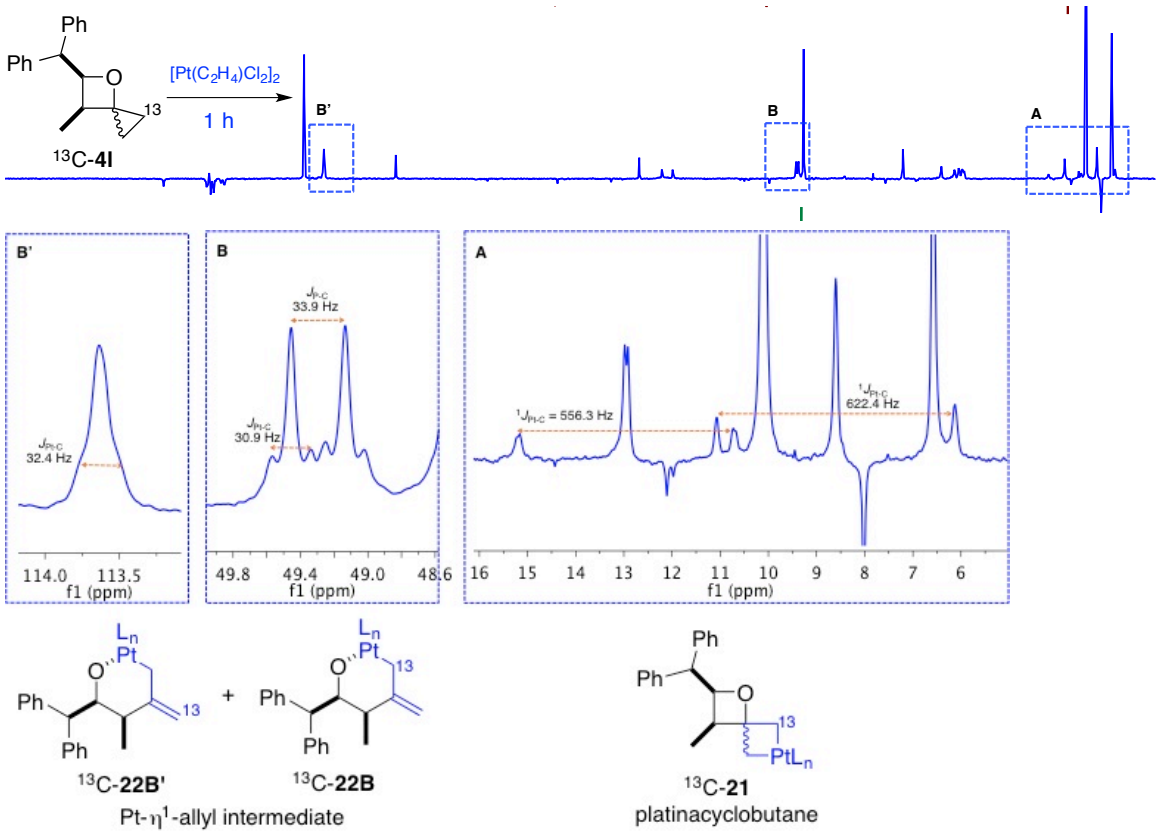
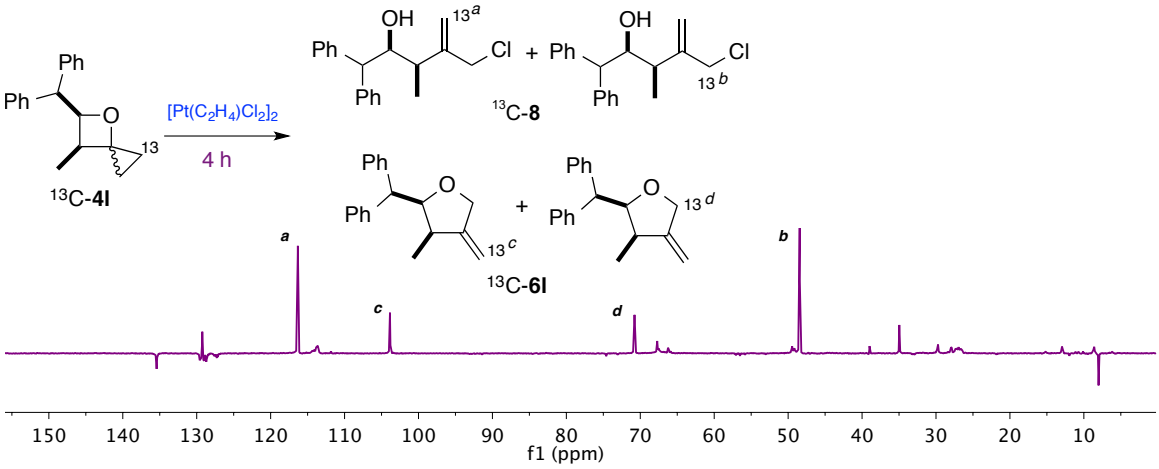


Figure 10b. ^{13}C DEPT NMR (CD_2Cl_2, room temp., 100 MHz) of the reaction after **4 h**:

The labeled peaks correspond to the ^{13}C-labeled carbons in compounds ^{13}C-**11** and ^{13}C-**6l** as major and minor products (no purification was done). As reference, compound **4l** was treated in the same conditions and compounds **8** and **6l** were isolated in 52% and 16% yields, respectively.



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Chapter 2

Transition Metal Catalyzed Transformations of α-Methylene-β-lactones

2.1 Introduction

β-Lactones are an important class of heterocyclic compounds found in several synthetic and natural products of biological relevance.[1-4] For instance, orlistat,[1] an FDA-approved drug for the treatment of obesity, contains a β-lactone which was found to be associated with its activity as a pancreatic lipase inhibitor (Figure 11). Orlistat (tetrahydrolipstatin) is a synthetic product derived from the modification of its natural product analog, lipstatin. Other β-lactone-containing natural products of biological importance include salinosporamide A,[2] a potent anticancer agent, and obafluorin,[3] a natural product with moderate antibacterial activity.

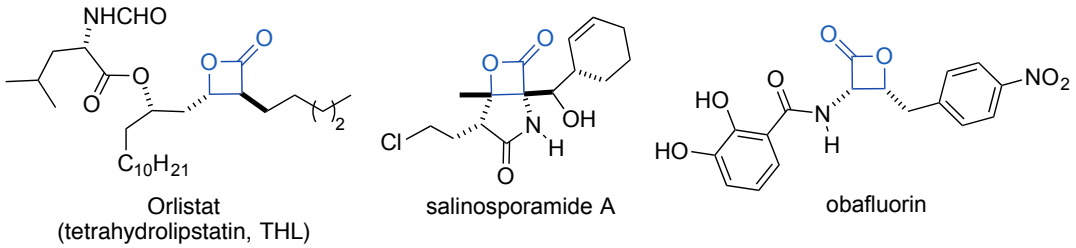
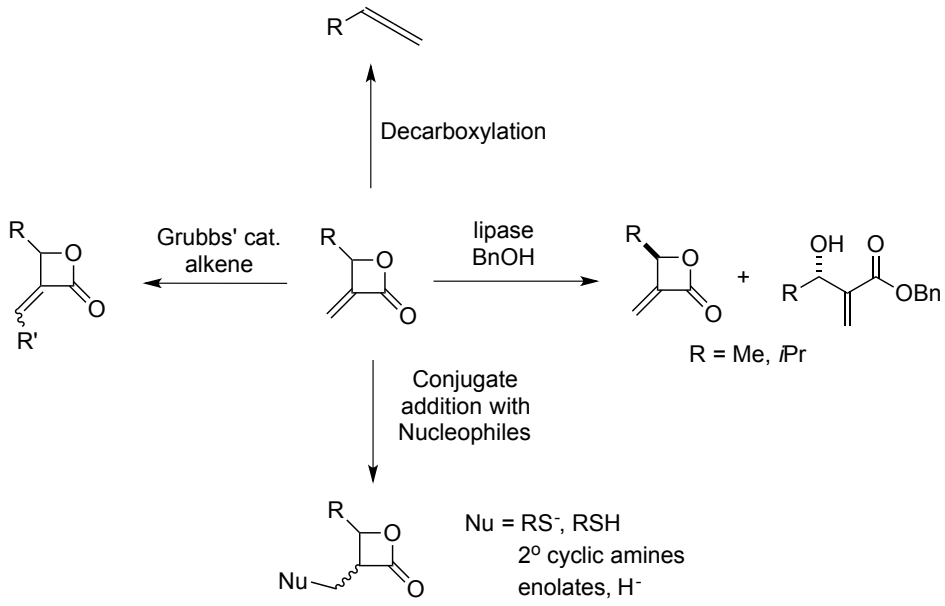


Figure 11. Selected biologically active natural and synthetic β-lactones.

Aside from the prevalence of β-lactones in natural products, they are considered privileged intermediates in organic synthesis as they offer a broad range of reactivities.[5] The Howell group has recently utilized a particular class of β-lactones, α-methylene-β-lactones, in a ruthenium catalyzed cross-metathesis reaction[6,7] that provided access to a library of disubstituted β-lactones (Scheme 38). Some of these lactones were recently evaluated in activity-based protein profiling (ABPP) studies as small molecule inhibitors of fatty acid synthase (FAS) and phosphatidylserine (PS) lipase.[7] Other previous reports on the reaction of α-methylene-β-lactones (Scheme 38) include: (a) Michael addition with cyclic secondary amines,[8] thiolates[8] and enolates[9] (b) enzymatic transesterification with alcohols,[10] and (c) thermal decarboxylation to allenes.[11]



Scheme 38. Previous reports on the reactions of α-methylene-β-lactones.

The belief that α-methylene-β-lactones are advantaged intermediates in the construction of valuable products led this work to explore their reactivities under transition metal catalysis. This chapter consists of two successful transition metal catalyzed transformations of α-methylene-β-lactones. First is a rhodium catalyzed conjugate addition with aryl boronic acids to access *trans*- and *cis*-β-lactones. Second, a chemoselective amidation with amines via a palladium catalyzed acyl C–O bond activation is described.

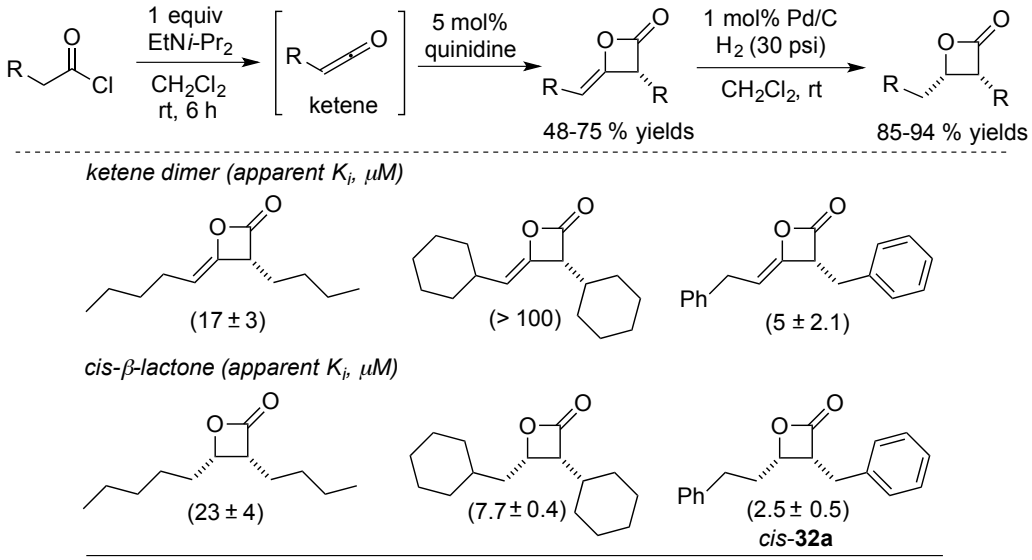
2.2 Rhodium Catalyzed Conjugate Addition of Aryl Boronic Acids to α-Methylene-β-lactones

2.2.1 Background and Significance

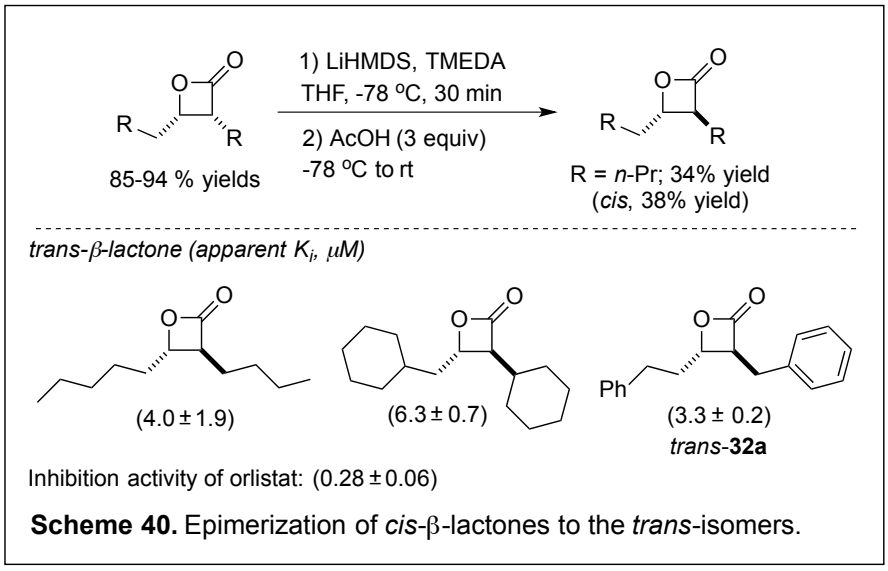
2.2.1.1 Approaches to disubstituted β-lactones

The recent finding that orlistat (see Figure 11), a disubstituted *trans*-β-lactone, is a potent inhibitor of FAS (fatty acid synthase) led to the development of practical routes to various disubstituted β-lactones.[1] The well-documented up-regulation of FAS in cancer cells makes this enzyme an interesting therapeutic target for cancer treatment.[12,13] The Howell group and others have reported methods to easily construct various disubstituted β-lactones as small molecule inhibitors of FAS or other serine/threonine proteases.

The Romo group[14] reported a route to disubstituted β-lactones based on a two-step process involving Calter's[15] organocatalytic, asymmetric ketene dimerization of acid chlorides followed by a facial-selective hydrogenation leading to *cis*-substituted-β-lactones. (Scheme 39). Several acyl chlorides underwent quinidine catalyzed ketene dimerization and gave isolable β-alkylidene-β-lactones in good enantioselectivities. Hydrogenation of the ketene dimers under Pd catalysis provided *cis*-β-lactones with excellent diastereoselectivities. Subsequent base mediated α-epimerization allowed access to *trans*-β-lactones, albeit with low diastereoselectivities (Scheme 40). This two step process provided a practical approach to simple, pseudosymmetric dialkyl β-lactones. Products obtained from this protocol were evaluated for FAS inhibition. β-Lactone **32a** (both *cis* and *trans*, Schemes 39 and 40) displayed significant FAS inhibitory activities, only 10-fold lower than that of orlistat. The promising FAS inhibitory activity displayed by simple, disubstituted β-lactones opens opportunities specifically in developing other methods than can provide access to a more diverse range of β-lactones.



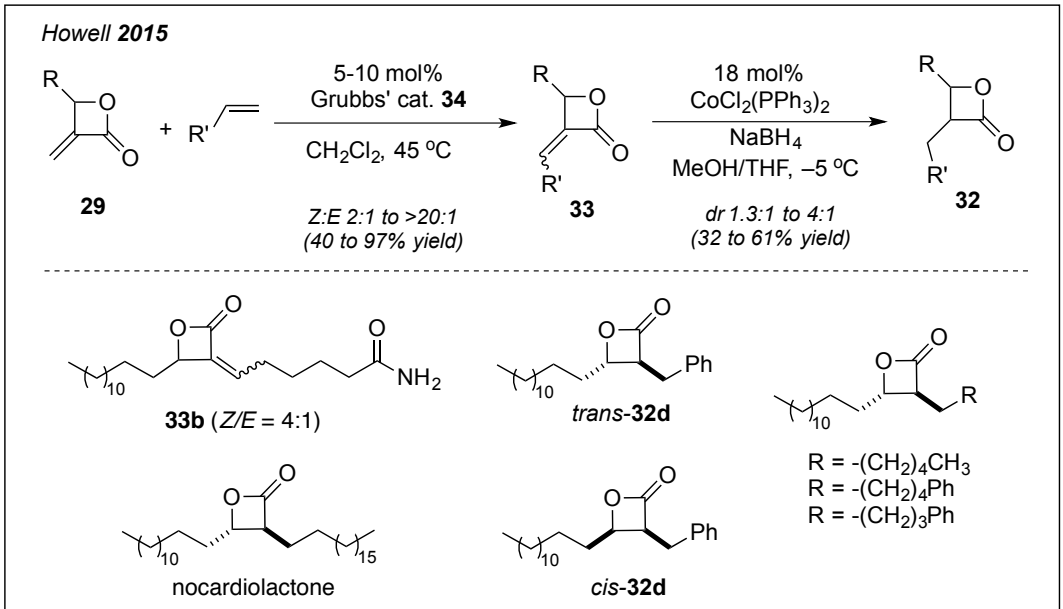
Scheme 39. β-Lactone synthesis by ketene dimerization/hydrogenation sequence.



Scheme 40. Epimerization of *cis*-β-lactones to the *trans*-isomers.

In exploring the reactivities of strained heterocycles with exocyclic unsaturation, the Howell group found that α-methylene-β-lactones **29** participated in cross-metathesis (CM) reactions with Type I alkenes,[16] with couplings proceeding in high yields and with excellent *Z*-stereoselectivities.[6] This method was recently utilized to access a wide range of previously

unexplored β-lactones for their evaluation as electrophilic probes or inhibitors of FAS and other related enzymes, particularly in the serine/threonine hydrolase class.[7,17]



Scheme 41. β-Lactone synthesis by cross-metathesis/reduction sequence.

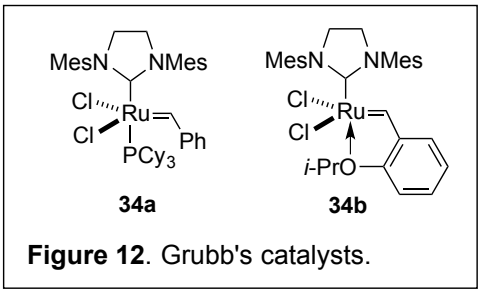


Figure 12. Grubb's catalysts.

The methodology described above is an attractive approach to a focused library of β-lactones for several reasons. First, the α-alkylidene-β-lactones can be used as probes. In a recent report from the Howell and Cravatt groups,[17] α-alkylidene-β-lactone **33b** was identified as a potent inhibitor of ABHD16A, a poorly characterized enzyme found to regulate immunomodulatory lysophosphatidylserines (*lyso*-PS). Moreover, the identification of lactone **33b** as an inhibitor facilitated the functional characterization of the ABHD16A. Secondly, the α-alkylidene-β-lactones can be converted selectively to *trans*- or *cis*- β-lactones via diastereoselective reductions. *cis*-β-Lactones were accessed by hydrogenation reactions. The

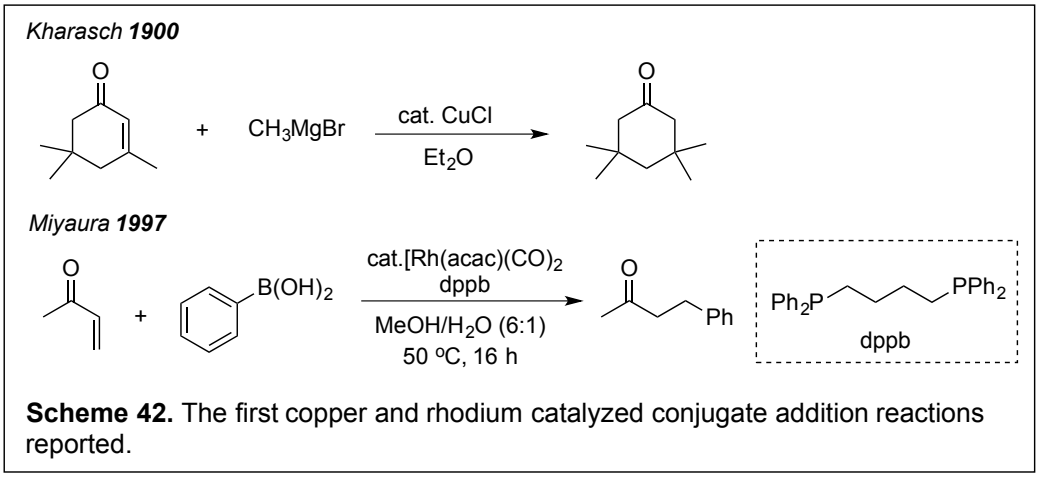
trans-isomers were obtained via a cobalt catalyzed 1,4-reduction in good yields, albeit, with moderate diastereoselectivities.[7]

The β-lactones obtained were screened as probes in a competitive ABPP assay against several serine hydrolase targets in the mouse brain membrane proteome. Among the β-lactones, *trans*-**32d** displayed one of the broadest reactivity profiles against detected serine hydrolase targets. Specifically, *trans*-**32d** potently inhibited FAS, ABHD16A, and six other enzyme targets. The promising activities exhibited by β-lactones, in particular, disubstituted β-lactones, as inhibitors of serine hydrolases exposes the need to prepare diverse analogs of these compounds. While the utility of α-methylene-β-lactones in CM/reduction sequence provides access to diverse disubstituted β-lactones, we hoped that these intermediates could also be used in conjugate addition reactions.[18,19] However, conjugate addition reactions typically require strong nucleophiles that might potentially cause the β-lactones to undergo ring opening reactions. Nonetheless, promising conjugate addition reactions have been developed, including rhodium-catalyzed conjugate additions of aryl boronic acids. Examples of these type of reactions and potential application to α-methylene-β-lactones are summarized in the next section.

2.2.1.2 Rhodium catalyzed conjugate addition of aryl boronic acids

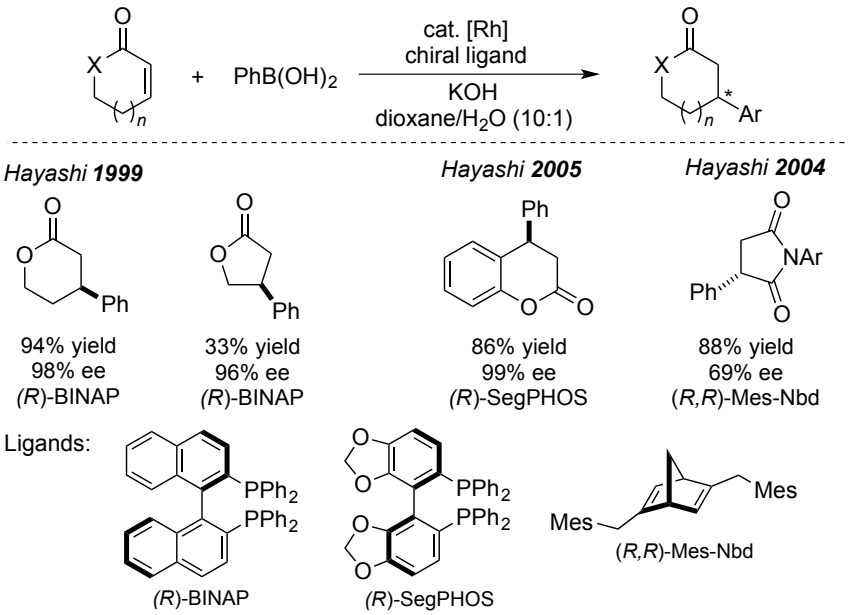
Catalytic conjugate addition reactions of organometallic reagents to enones has emerged as a fundamental methodology in the construction of C-C bonds.[18,19] This type of reaction has been known since 1900 when Kharash[20] reacted isophorone with methyl Grignard reagent in the presence of catalytic amount of copper chloride (Scheme 42). Other metal complexes, such as those of Ni and Pd, were reported to effect similar transformations.[21,22] However, with these catalysts, air and moisture sensitive organometallic coupling partners

(Grignard or organolithium reagents, enolates) are required, leading to difficulty in handling and manipulation of reactions, as well as problems with broad functional group tolerance.



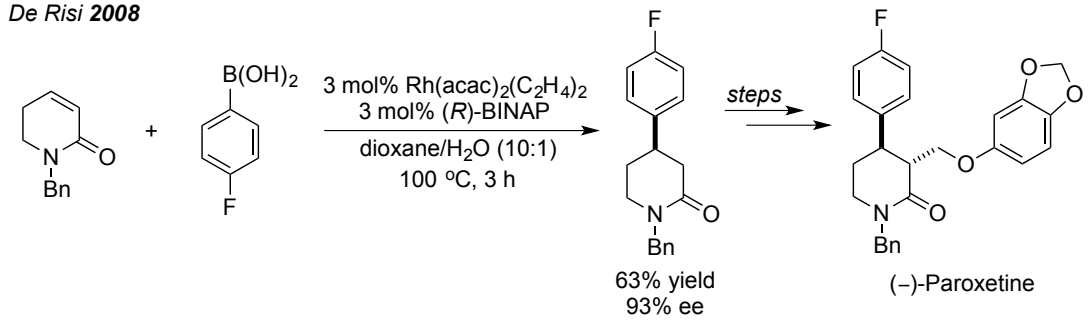
Scheme 42. The first copper and rhodium catalyzed conjugate addition reactions reported.

Miyaura and co-workers[18] reported the first conjugate addition reaction to an enone (methyl vinyl ketone) with phenyl boronic acid under rhodium catalysis (Scheme 42). In contrast to previous transition metal catalyzed conjugate additions, the reaction was done in the presence of water as co-solvent. In the last two decades, rhodium catalyzed conjugate addition has witnessed advancements. In particular, new rhodium complexes and organoboron reagents have been developed.[19,23] Likewise, various substrates, including α,β-unsaturated esters, amides, lactones, lactams, nitriles, and aldehydes, have been utilized.[19]



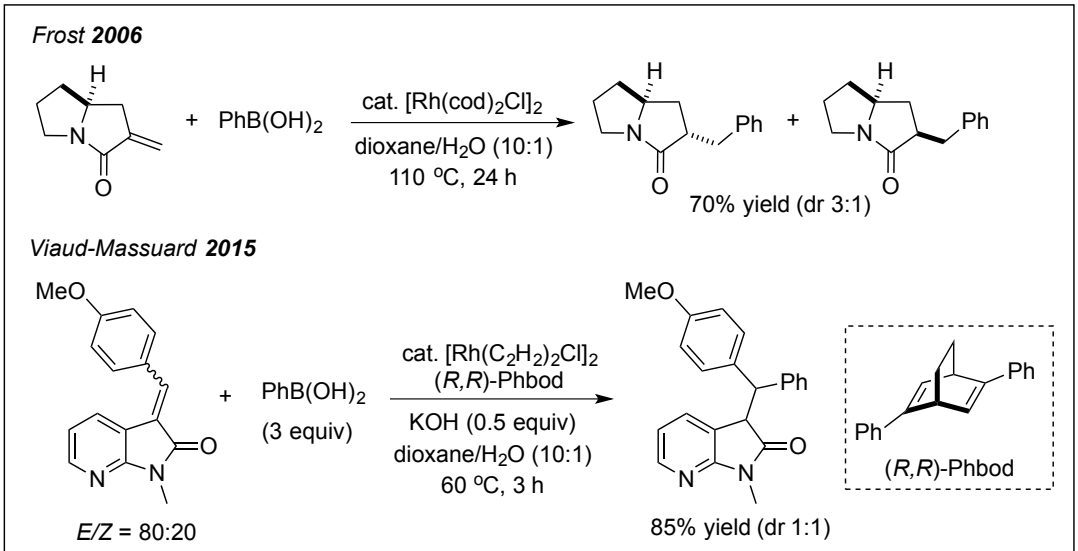
Scheme 43. Selected examples of Rh-catalyzed conjugate addition of aryl boronic acids with α,β-unsaturated lactones and lactams.

Hayashi and co-workers[24-26] pursued the rhodium catalyzed conjugate addition of aryl boronic acids to endocyclic α,β-unsaturated lactones and lactams. Selected examples of products obtained through this process are shown in Scheme 43. Most examples provided products in excellent yields, and in the presence of appropriate chiral ligands, high enantioselectivities were achieved. In the case of γ-butyrolactone, the low yield obtained was thought to be associated with potential instability of the 5-membered lactone under the conditions (use of KOH, reaction temperature up to 100 ^{o}C). Dihydropyridinones were also utilized in Rh-catalyzed conjugate additions to access 4-arylpiperidinones.[27] The 4-arylpiperidinone shown in Scheme 44 is a known intermediate in the synthesis of (–)-paroxetine,[28] a drug used for the treatment of Parkinson's disease.



Scheme 44. Rh-catalyzed conjugate addition to dihydropyridinone for the synthesis of (–)-paroxetine.

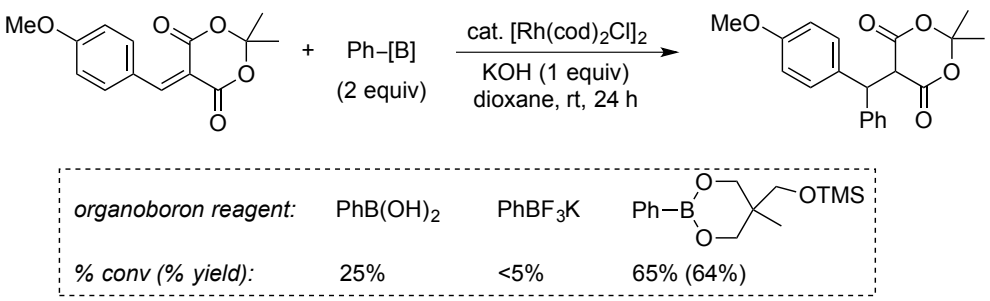
The conjugate addition reactions to exocyclic α,β-unsaturated lactones and lactams under rhodium catalysis with organoboron reagents is rare. Frost and co-workers[29] reported 1,4-additions with α-methylenepyrrolizidinones that provided products in good yields with modest selectivity towards the *trans*-adduct (Scheme 45). Very recently, Viaud-Massuard and co-workers[30] disclosed the conjugate addition of aryl boronic acids with α-benzylidene-7-azaoxindoles.



Scheme 45. Rhodium catalyzed conjugate addition of exocyclic lactams with aryl boronic acids.

Frost[30] also pursued a Rh-catalyzed conjugate addition to benzylidene dilactones derived from Meldrum's acid (Scheme 46). One challenge associated with this type of

substrate is its instability with nucleophiles, including water, requiring the need for anhydrous conditions.[31] Aryl boronic acids and potassium trifluoroborate salts were found ineffective, presumably due to their low solubility in organic solvents. However, novel TMS-protected aryl dioxaborinanes yielded desired products in moderate yields.

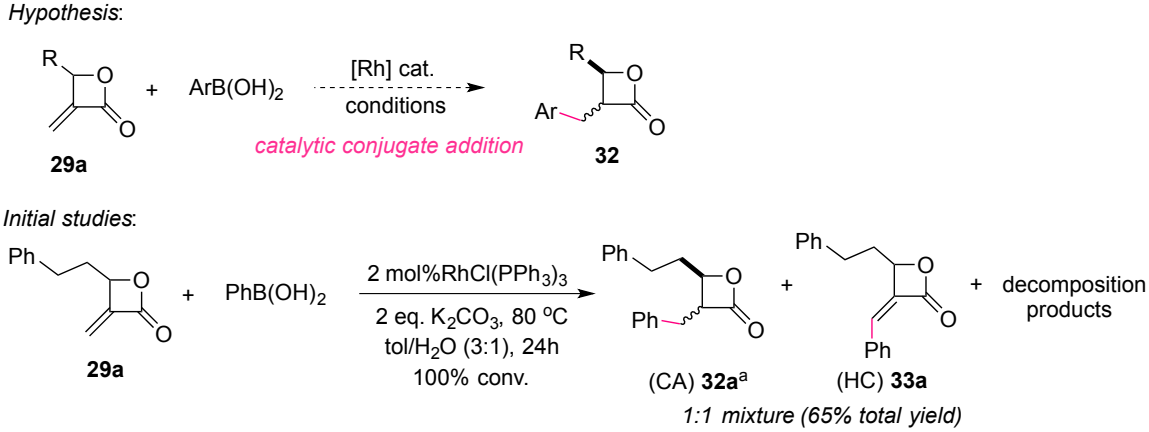


Scheme 46. Rhodium catalyzed conjugate addition of benzylidene Meldrum's acid with organoboron reagents.

These successful reports of Rh-catalyzed conjugate addition reactions to exocyclic α,β-unsaturated lactones and lactams provide openings, in particular, to four-membered heterocyles. To our knowledge, there has been no report of Rh-catalyzed conjugate addition reactions to exocyclic α,β-unsaturated β-lactones or β-lactams. We envisioned that α-methylene-β-lactones could undergo Rh-catalyzed conjugate addition with aryl boronic acids. However, potential challenges were anticipated. First, β-lactones could undergo ring opening reactions under basic conditions, elevated temperatures and in aqueous solutions. Second, as described in Scheme 45, the diastereoselectivity of this type of reaction could be difficult to control. In the next sections, we describe the development of a rhodium catalyzed conjugate addition reactions of α-methylene-β-lactones with aryl boronic acids. The optimization and scope of the reactions were investigated.

2.2.2 Mechanistic Hypothesis and Initial Studies

Inspired by the biological activities displayed in disubstituted β-lactones and the advancement in Rh-catalyzed conjugate additions, it was hypothesized that α-methylene-β-lactones **29** would undergo conjugate addition with organoboron reagents (Scheme 47). To test this hypothesis, α-methylene-β-lactone **29a** was reacted with phenyl boronic acid in the presence of Wilkinson's catalyst.[33] This initial reaction provided a mixture of the desired conjugate addition product, β-lactone **32a**, together with the Heck-type product α-alkylidene-β-lactone **33a** (Scheme 47). The Rh-catalyzed conjugate addition to give β-lactone **32a** constitutes a one-step process for disubstituted β-lactones from α-methylene-β-lactones, in contrast to the cross-metathesis/reduction sequence our group previously reported. However, the results from the initial studies required optimization in order to: (a) selectively obtain conjugate addition product, (b) prevent decomposition, and (c) improve the diastereoselectivity of the reaction.



Scheme 47. Hypothesis and initial studies on the Rh-catalyzed conjugate addition for direct access to disubstituted β-lactones.
[a]The obtained *trans:cis* ratio was 2:1.

Herein we report a strategically distinct, one-step approach to access disubstituted β-lactones from α-methylene-β-lactones. Optimization of reaction conditions to improve selectively towards conjugate addition, as well as an exploration of the scope and limitations

of the reaction, are presented in the following sections.

2.2.3 Results and Discussions

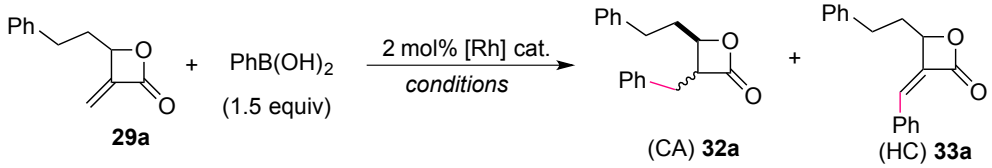
2.3.4.1 Optimization of reaction conditions

At the onset of this study, we realized two challenges. First, α-methylene-β-lactones and their corresponding products are highly susceptible to nucleophilic attack (e.g. with water or base additives) either via conjugate addition or ring-opening reactions. Second, based on the initial reaction conducted by reacting α-methylene-β-lactone **29a** with phenyl boronic acid using Wilkinson's catalyst as the rhodium source,[33] an equal mixture of conjugate addition and Heck-type product was obtained. The formation of Heck-type products in Rh-catalyzed reactions was previously observed when α,β-unsaturated esters and amides were used.[33] This competitive pathway was proposed to occur via β-hydride elimination (versus protonolysis) from the α-metallated intermediate. However, with α,β-unsaturated esters and amides the conjugate addition products can be selectively obtained by using appropriate conditions.

Several parameters evaluated included rhodium catalyst, temperature, solvent system, and base additives. Table 5 summarizes the results of the preliminary screening. Using Wilkinson's catalyst as the rhodium source, a complete conversion was observed. However, a 1:1 mixture of conjugate addition and Heck-type coupling product was obtained together with unidentified decomposition products. When a lower temperature (60 ^{o}C) was employed, no significant conversion was observed after 24 h.

Gratifyingly, improved results were obtained when the rhodium dimer, $[Rh(cod)Cl]_2$ was utilized under the conditions independently developed by Hayashi and Miyaura.[19,23] In contrast to the use of Wilkinson's catalyst, the reaction was rendered more efficient, having faster reaction time and cleaner conversion. However, the ratio of CA/HC (conjugate addition/Heck-coupling) was found to be 2:1. Several additives or bases were screened

(entries 3–8), and it was found that in the presence of KOH in a stoichiometric or greater amount (1–2 equivalents), exclusive conversion to conjugate addition product was obtained after 1 h. It is worth noting that the β-lactones (starting material or product) did not undergo ring opening reactions under the basic conditions. The conjugate addition product **32a** was isolated in 92% yield with a *trans*:*cis* ratio of 2:1. Moreover, the reaction could also be achieved using 1 mol% Rh catalyst providing similar results.



Entry	Rh catalyst	Conditions	[b]Conversion, time	[c]CA:HC
1	$RhCl(PPh_3)_3$	2 eq. K_2CO_3, 80 °C	100%, 24h	1:1 (with decomposition)[d]
2	$RhCl(PPh_3)_3$	2 eq. K_2CO_3, 60 °C	<5%, 24h	-
3	$[Rh(cod)Cl]_2$	2 eq. K_2CO_3, 60 °C	100%, 1h	2:1
4	$[Rh(cod)Cl]_2$	2 eq. KF, 60 °C	30%, 24h	1:1
5	$[Rh(cod)Cl]_2$	2 eq. KOH, 60 °C	100%, 1h	>20:1 (60% yield)[d]
6	**$[Rh(cod)Cl]_2$**	**1 eq. KOH, 60 °C**	**100%, 1h**	**>20:1 (92% yield)[d]**
7	$[Rh(cod)Cl]_2$	0.5 eq. KOH, 60 °C	100%, 1h	3.5:1
8	$[Rh(cod)Cl]_2$	0.1 eq. KOH, 60 °C	100%, 48h	2:1
9	$[Rh(cod)Cl]_2$	1 eq. KOH, r.t.	75%	5:1
10	$RhCl(PPh_3)_3$	1 eq. KOH, 60 °C	100%, 24h	2:1
11	$[Rh(nbd)Cl]_2$	1 eq. KOH, 60 °C	100%, 1h	>20:1 (90% yield)[d]

*Solvent: entries 1 to 3, toluene/H_2O (3:1); entries 4 to 11, dioxane/H_2O (10:1)

[a]Reaction conditions: 0.5 mmol 29a, 0.75 mmol $PhB(OH)_2$, 2 mol% Rh catalyst. Yields were isolated yields.
[b]Percent conversion based from ^1H NMR analysis of the crude mixture.
[c]CA:HC, ratio of conjugate addition and Heck coupling products based from ^1H NMR analysis of the crude mixture.
[d]The obtained *trans:cis* ratio was 2:1.

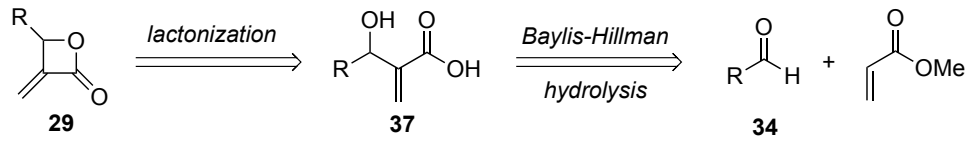
Table 5. Initial studies on the Rh-catalyzed conjugate addition of phenyl boronic acid to **29a**.

Further optimization studies were conducted to improve the diastereoselectivity of this method using various conditions (entries 7–11); however, no significant improvement was observed. The formation of both diastereomers could presumably arise from the protonolysis

step, similar to the Co-catalyzed reduction of α-alkylidene-β-lactones we have previously reported.[7] Nonetheless, the optimized conditions above represent a simple, one-step access to the desired disubstituted β-lactones from α-methylene-β-lactones.

2.3.4.2 Preparation of α-methylene-β-lactones

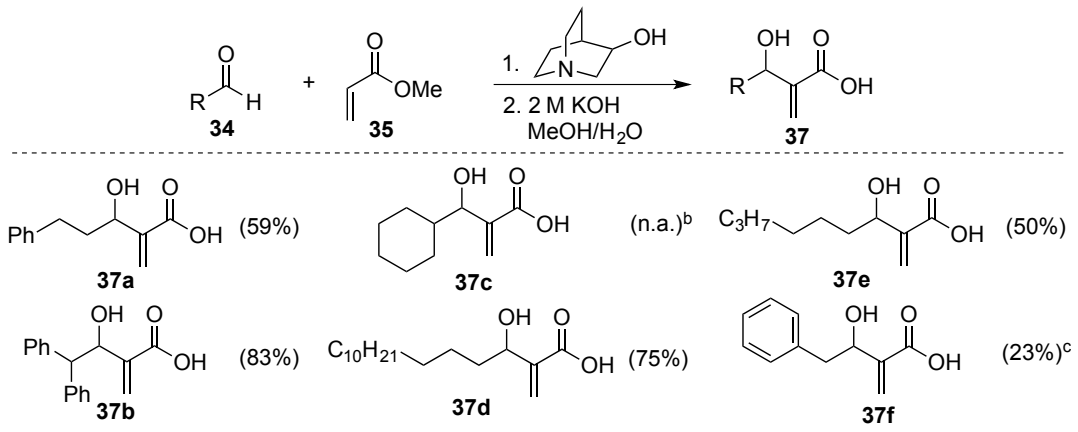
A variety of α-methylene-β-lactone substrates was readily prepared from lactonization of α-methylene-β-hydroxy acids **37**.[34,35] β-Hydroxy acids were accessed from a one-pot, 2-step reaction sequence involving Morita-Baylis-Hillman (MBH) reaction of aldehydes and methyl acrylate, followed by hydrolysis.[34,36]



29 **37** **34**

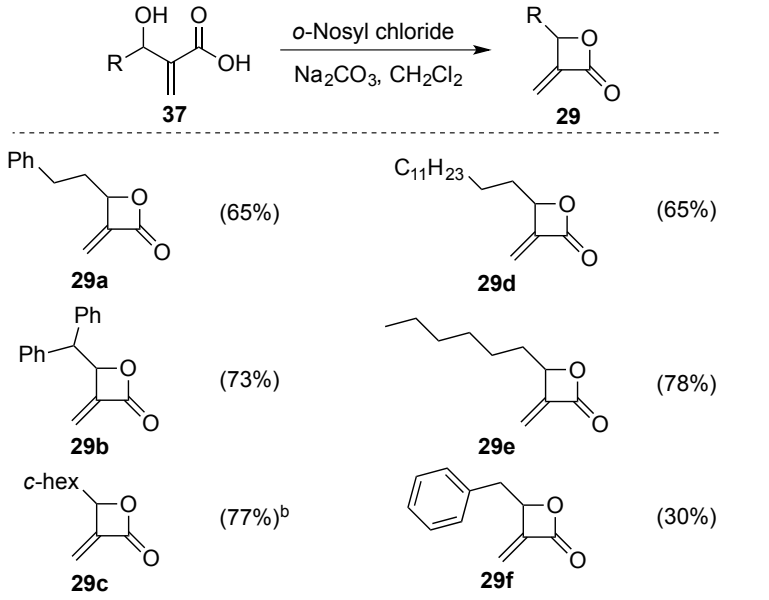
Scheme 48. Retrosynthesis of α-methylene-β-lactones **29**.

The MBH adducts were obtained quantitatively in 2 days by using catalytic amounts of 3-quinuclidinol as the organocatalyst. DABCO could also be used and provided similar results, but typically required much longer reaction times (1–2 weeks).[34] Hydrolysis of the MBH adducts gave β-hydroxy acids in good yields over 2-steps (Table 6a). β-Hydroxy acid **37f** was obtained in low yields. This was due to the formation of an aldol condensation product during the MBH step with quinuclidinol after 3 h. Other organocatalysts, including DABCO, DBU and triphenylphosphine, were examined; however, inferior results were obtained. A nosyl chloride mediated lactonization[34] provided desired α-methylene-β-lactones **29** in moderate to good yields (Table 6b).



[a]Values in parentheses are isolated yields in 2-steps. [b]Product **37c** was not purified and was carried through the next step. [c]Low isolated yield was associated with the MBH step where aldol condensation product was also obtained.

Table 6a. MBH/hydrolysis sequence to obtain β-hydroxy acids **37**.



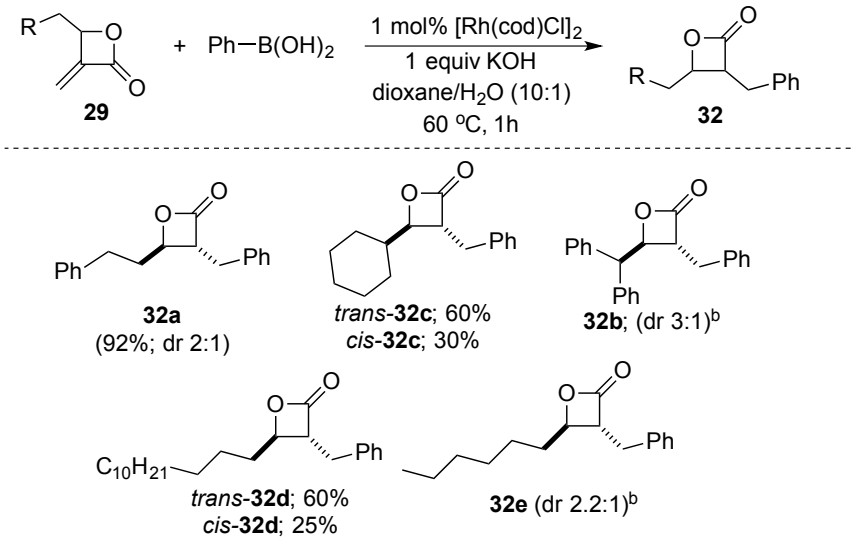
[a]Values in parentheses are isolated yields in 2-steps.

[b]Yield of **29c** was over 3-steps.

Table 6b. *o*-Nosyl chloride mediated lactonization of β-hydroxy acids **37** to α-methylene-β-lactones **29**.

2.3.4.4 Scope and limitation of the reaction

After accessing α-methylene-β-lactones with various β-chains, and with the optimal conditions in hand, the scope of the rhodium catalyzed conjugate addition reaction was explored (Scheme 49). α-Methylene-β-lactones with various β-chains reacted with phenyl boronic acid and gave their corresponding disubstituted β-lactone products in good to excellent yields. Almost complete selectivities (>20:1) towards conjugate addition products were observed in all cases. In these examples, diastereoselectivies ranged from a 2:1 to 3:1 (*trans*:*cis)* ratio. It is worth noting that β-lactones **32a**[14a] and *trans*-**33d**[7] were previously reported to have promising inhibitory activities against serine hydrolases.

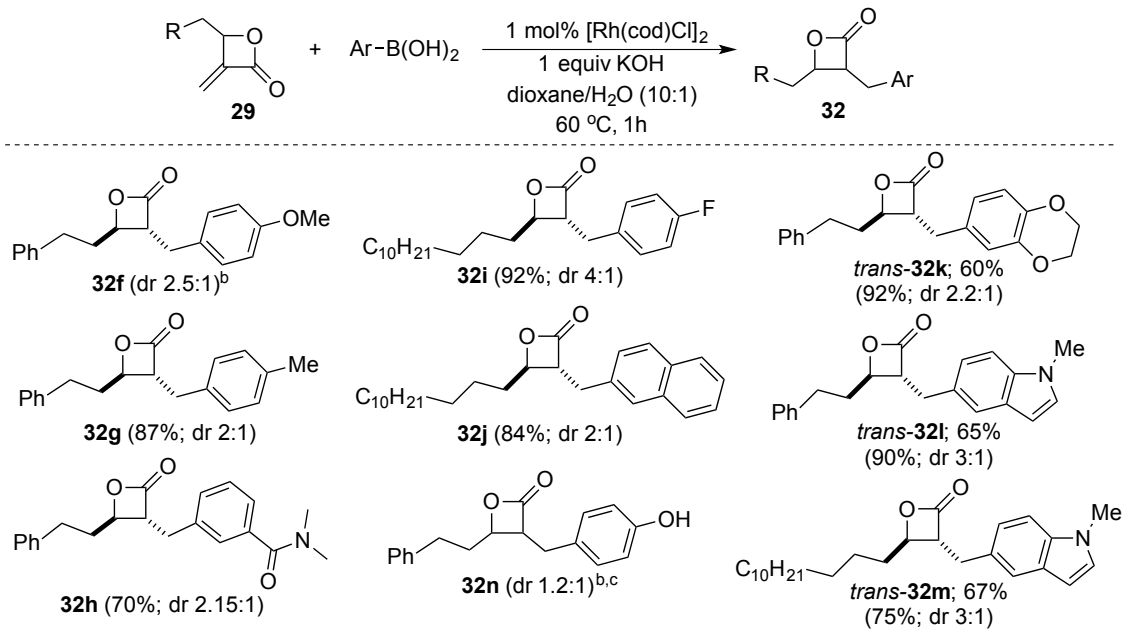


[a]Typical reaction conditions: 0.5 mmol 29, 0.75 mmol $PhB(OH)_2$, 1 mol% $[Rh(cod)Cl]_2$, 1 equiv KOH in 2.5 mL dioxane/H_2O (10:1) at 60 °C for 1h. In all cases, the CA:HC selectivity is >20:1. Yields are isolated yields; dr are diastereomeric ratios based from ^1H NMR analysis. Structure drawn represents the major diastereomer obtained.
[b]Products were not isolated, dr values were obatined based from ^1H NMR analysis of the crude mixture.

Scheme 49. Scope of the reaction of phenyl boronic acid with α-methylene-β-lactones.

Investigation of the scope of the conjugate addition reaction was also extended to various aryl boronic acids. The results are summarized in Scheme 49. Several coupling partners, including electron rich and electron deficient aryl boronic acids, were tolerated, providing products in good yields. To further exemplify the scope of the reaction, heteroaryl

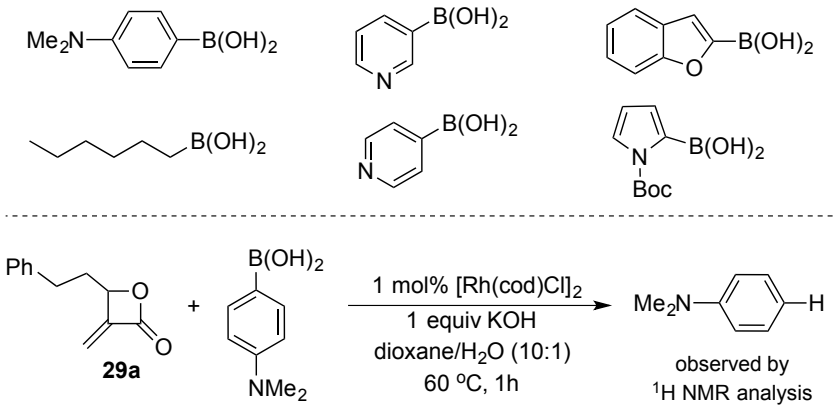
boronic acids as coupling partners were explored. *N*-Methyl indole and benzodioxan were successfully incorporated into the β-lactones. These examples are notable since both heterocycles are often found in biologically active products. Likewise, their incorporation into the β-lactone motif through the CM/reduction sequence could be challenging due to the lack of availability of necessary olefin coupling partners.



[a]Typical reaction conditions: 0.5 mmol 29, 0.75 mmol $PhB(OH)_2$, 1 mol% $[Rh(cod)Cl]_2$, 1 equiv KOH in 2.5 mL dioxane/H_2O (10:1) at 60 °C for 1h. In all cases, unless specified, the CA:HC selectivity is >20:1. Yields are isolated yields. Values in parenthesis are mixed isolated yields of both isomers; dr is diastereomeric ratio. Structure drawn represents the major diastereomer obtained.
[b]Products were not isolated, dr values were obatined based from ^1H NMR analysis of the crude mixture.
[c]The CA:HC selectivity was 11:1.

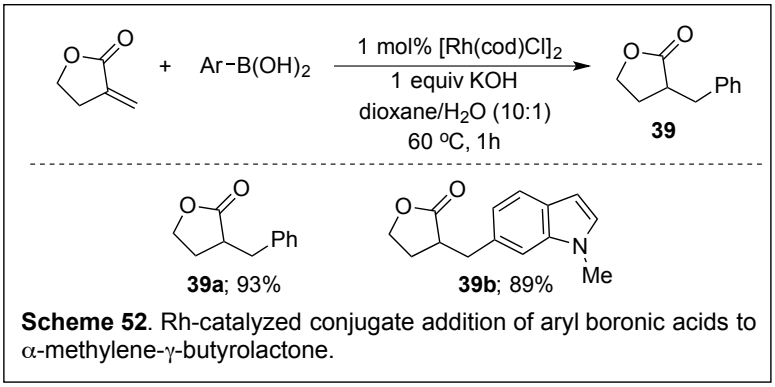
Scheme 50. Scope of the reaction of α-methylene-β-lactones with various aryl boronic acids.

α-Methylene–β-lactones did not convert into products when coupling was attempted with some organoboron compounds, including alkyl boronic acid, *N,N*-dimethylaminophenyl boronic acid, and several heteroaryl boronic acids. However, the organoboron reagents were consumed, and in several cases protodeborylated products were observed based on ^1H NMR analysis of the reaction mixture. These exceptions could be explained by the propensity of the organoborons to undergo protodeborylation reactions, outcompeting conjugate addition, especially under aqueous conditions.



Scheme 51. Selected aryl boronic acids explored that did not undergo conjugate addition with **29a**.

The rhodium catalyzed conjugate addition reaction was extended to the five-membered α-methylene-γ-butyrolactone. Arylated γ-lactone products **39a** and **39b** were obtained using the same protocol in excellent yields up to 93% (Scheme 52).

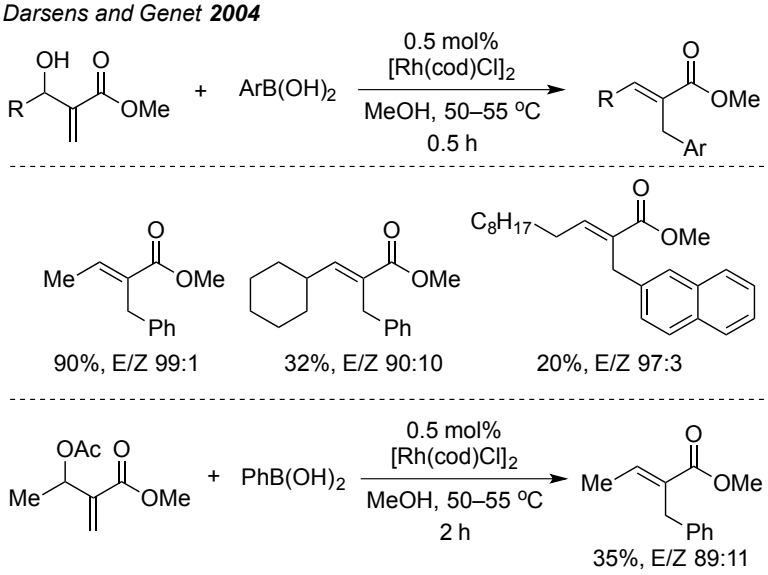


Scheme 52. Rh-catalyzed conjugate addition of aryl boronic acids to α-methylene-γ-butyrolactone.

The protocol described above demonstrated high selectivity towards conjugate addition over Heck-type coupling reactions. It also worth mentioning that an exclusive chemoselectivity towards conjugate addition was observed over reaction at other several potential electrophilic sites present in α-methylene–β-lactones.[7,8-10]

α-Methylene-β-lactones are viewed as masked MBH adducts. Darses and Genet[37,38] reported that, when acyclic MBH adducts were treated with aryl boronic acids using similar rhodium catalysts, in sharp contrast to the results obtained above, trisubstituted alkenes were obtained (Scheme 52). This outcome was observed even when the reaction conditions were

varied to different rhodium catalysts, solvents and types of organoboron reagent.[38] When the acetate of a MBH adduct was utilized, lower reactivity was observed. However, the same product was obtained (Scheme 53). The observed reaction was believed to proceed via a mechanism involving conjugate addition with a subsequent β-hydroxy (or β-acetoxy) elimination steps.[37]



Scheme 53. Unexpected reaction pathway observed from MBH adducts and acetates under Rh-catalyed reaction with aryl boronic acids.

2.3.4.4 Proposed mechanism

Based on previous mechanistic information on rhodium catalyzed conjugate additions of aryl boronic acids to α,β–unsaturated systems,[19,23] together with several observations from control reactions conducted, the mechanism shown in Figure 13 is proposed. First, the active rhodium catalyst **I** is generated from transmetallation with KOH. Rh-complex **I** undergoes transmetallation with aryl boronic acid to form aryl-Rh complex **II**. Coordination to the olefin of the α-methylene-β-lactone with subsequent aryl migration will provide metallated lactone **III**. This metallated species could undergo hydrolysis to provide the β-lactone product with subsequent regeneration of the active Rh-complex **I**. The formation of the Heck-type *Z*-

alkylidene β-lactone product can be explained *via* a *syn* β-hydride elimination from metallated lactone **III**.

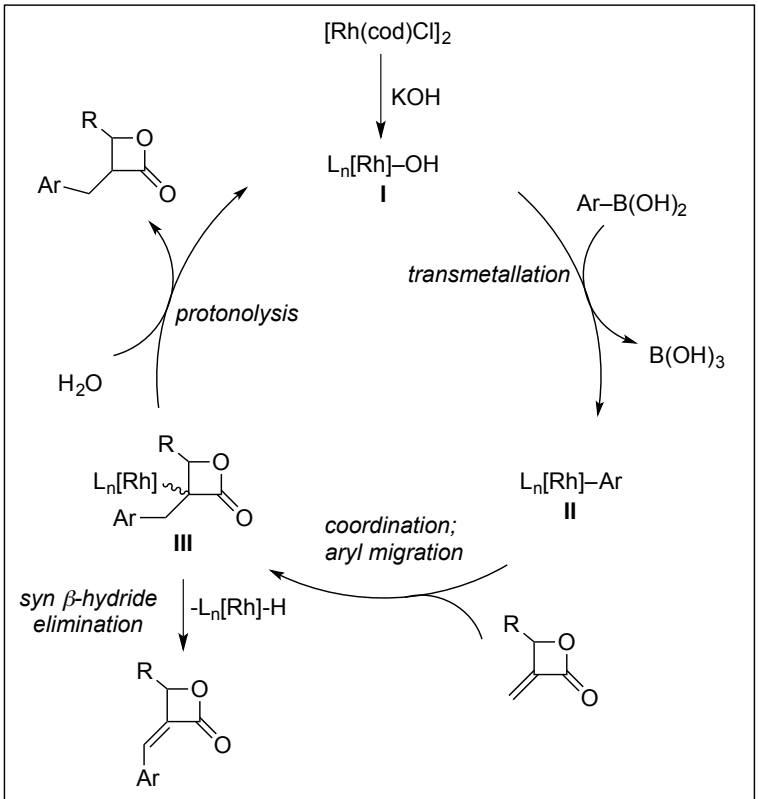


Figure 13. Proposed mechanism for the Rh-catalyzed conjugate addition reaction.

This proposed mechanism is consistent with several observations and previously reported mechanistic investigations. Some of these observations include: (a) the rhodium catalyst and KOH were necessary for the reaction; (b) the observation and isolation of protodeborylated products from the organoboron reagents suggest the formation of complex **II**, (c) and lastly, the formation of the conjugate addition and Heck-type coupling products can only both occur from the intermediacy of a metallated species like **III**.[33] At present, there is no evidence available to explain the observed selectivity towards conjugate addition over Heck-type coupling products.

The rhodium catalyzed conjugate addition of aryl boronic acids into α-methylene-β-lactones provided a one-step access to diverse disubstituted β-lactones. Reaction

optimization allowed the selective formation of the conjugate addition adduct over the Heck-type coupling product. Moreover, the reaction tolerated various types of aryl boronic acids. However, rendering the protocol to achieve better diastereoselectivities is still challenging.

2.3 Palladium Catalyzed Acyl C-O Activation of α-Methylene-β-lactones

2.3.1 Background and Significance

β-Lactones are increasingly utilized intermediates or scaffolds in organic synthesis (Figure 14).[5] This is mainly due to the many distinct reactions associated with the inherent ring strain exhibited by this heterocyle. One particularly interesting type of reaction associated with β-lactones is their ability to under ring-opening with various nucleophiles. Previously reported ring-opening reactions of β-lactones happen with good nucleophiles (e.g. alkyl amines, enolates, alkoxides and thiolate anions).[5] However, traditional ring-opening reactions of β-lactones with these types of nucleophiles typically suffer from poor regioselectivities, and the outcomes are hard to predict. In most cases, mixtures of two ring-opened products are obtained arising from either alkyl C-O bond cleavage or acyl C-O bond cleavage.

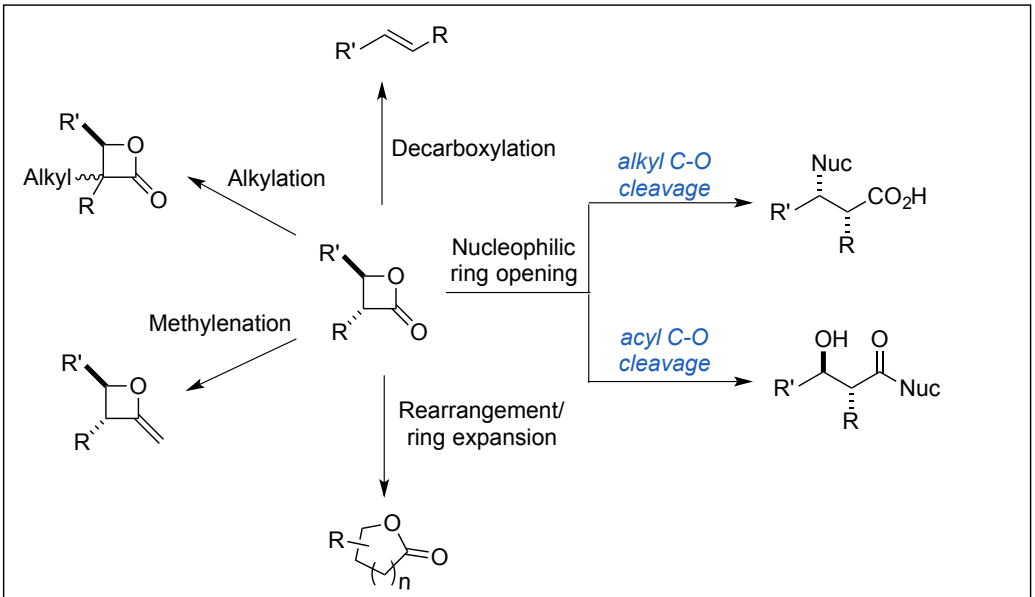
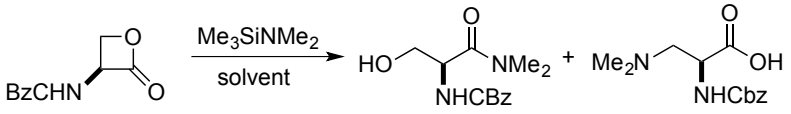


Figure 14. Selected reactions of β-lactones as precursors to functionalized intermediates.

One classic example that demonstrates the two competing ring opening pathways for β-lactones was described by Vederas and co-workers[39,40] in the reaction of serine-β-lactone with trimethylsilylamine (Scheme 54). The product distribution between alkyl C-O cleavage and acyl C-O cleavage showed a high solvent dependency; however, low to only moderate

selectivities were attained. Problems with regioselectivity in this type of reaction have been well-reviewed in the literature, and to date, there has been no practical solution that has met this challenge.[5]

Vederas ***1985***



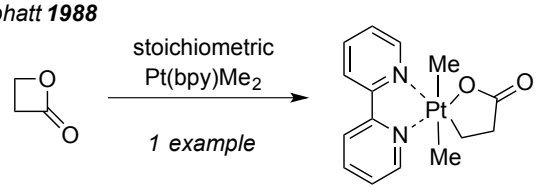
	product ratio
$CHCl_3$	*80:20*
DCM	*65:35*
THF	*20:80*

Scheme 54. Ring-opening reaction of β-lactone with amines.

Our interest in the utility of strained heterocycles, particularly β-lactones, led us to explore their potential regioselective ring-opening with nucleophiles. Recently, we have reported successful transformations of strained heterocycles under transition metal catalysis.[6,41,42] We envisioned that a selective cleavage of β-lactones, either at the alkyl or acyl C-O bond, should be achievable through transition metal catalysis.

To date, there are only a few reports on the opening of β-lactones using transition metals. Puddephatt[43] reported an alkyl C-O bond fission of oxetane-2-one with a stoichiometric amount of a Pt complex to form a platina-γ-lactone complex (Scheme 55).

Puddephatt ***1988***

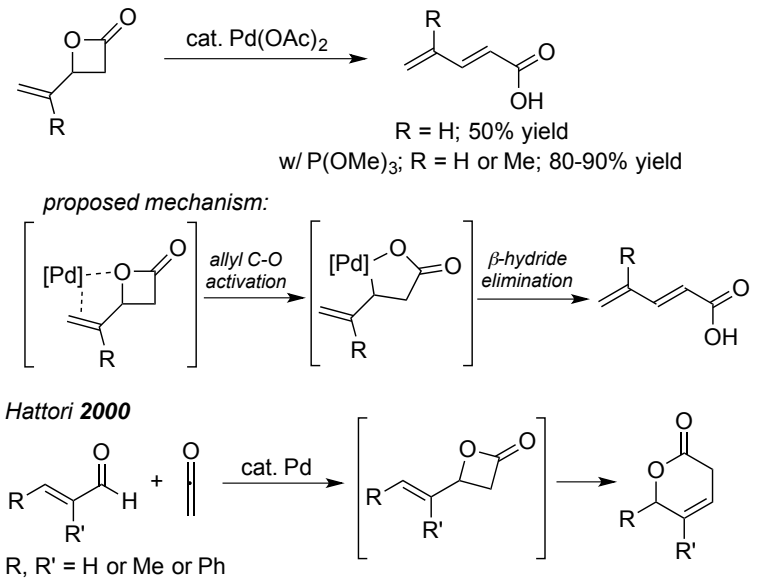


stable platinum (IV) complex

Scheme 55. Stoichiometric oxidative addition of Pt(II) to alkyl C–O bond of β-propiolactone to form platinalactone complex.

Noels[44] reported that vinyl-substituted β-lactones can be ring-opened to butadiene acids under palladium catalysis (Scheme 56). It was found that, when the reaction was conducted in the presence of trimethoxyphosphine, higher yields were obtained up to 90% (Scheme 56). An analogous reaction was reported by Hattori and co-workers (Scheme

56).[45,46] In this case, the vinyl β-lactones were generated in situ from the reaction of a ketene with an enal. In both reactions it was proposed that palladalactone intermediate is involved.[45] β-Hydride elimination (or cyclization) will lead to the formation of butadiene acid (or the 6-membered lactone).



Scheme 56. Pd-catalyzed ring-opening of vinyl β-lactones via an allyl C-O bond cleavage.

These examples of Pd-catalyzed activation of β-lactones were limited to alkyl C-O bond cleavage, in particular, allylic C-O bonds of a narrow group of β-lactones. To our knowledge, there have been no reports of TM-catalyzed activation of acyl C-O bonds in β-lactones. Consequently, we looked into TM-catalyzed acyl C-O bond activations of simple esters.

The TM-catalyzed activation of the alkyl C-O bond in esters is well document (Figure 15, path *a*). These type of reactions are typically observed in allylic systems (e.g. Tsuji-Trost allylation) or in aryl esters (as electrophiles in cross coupling reactions).[47] On the other hand, reports on TM-catalyzed activation of acyl C-O bond in esters are rare (Figure 15, path *b*).

One of the earliest reports on TM-catalyzed acyl C-O activation was developed by Yamamoto (Scheme 57).[48] This was demonstrated by the reaction of aryl trifluoroacetates with aryl boronic acids under palladium catalysis. It was proposed that the acyl C-O bond undergoes oxidative addition to Pd(0) to form a Pd(II) complex (Scheme 57). This complex then undergoes cross coupling reactions with aryl boronic acids to provide trifluromethyl aryl ketones.

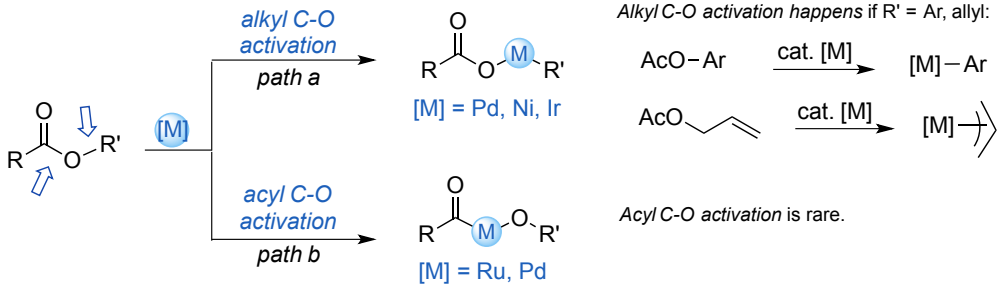
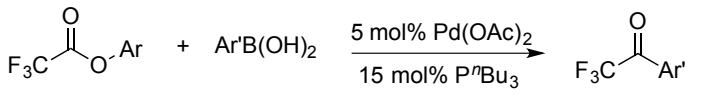
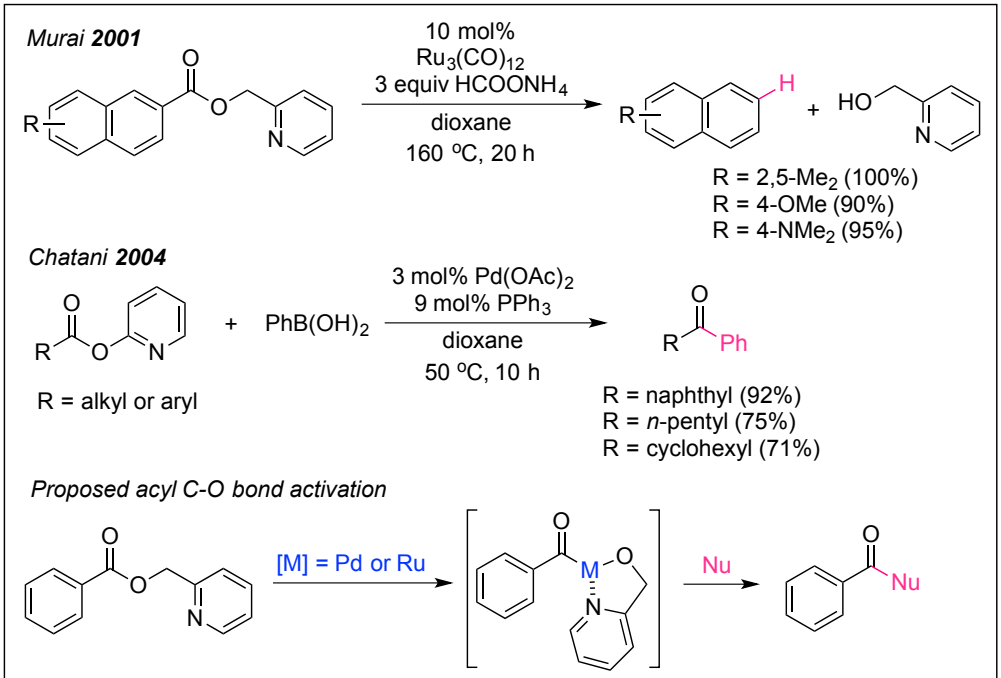


Figure 15. Inspiration from TM-catalyzed activation of esters: alkyl versus acyl C-O bond activation.



Scheme 57. Pd-catalyzed acyl C-O bond activation of aryl trifluoromethyl esters under Pd catalysis.

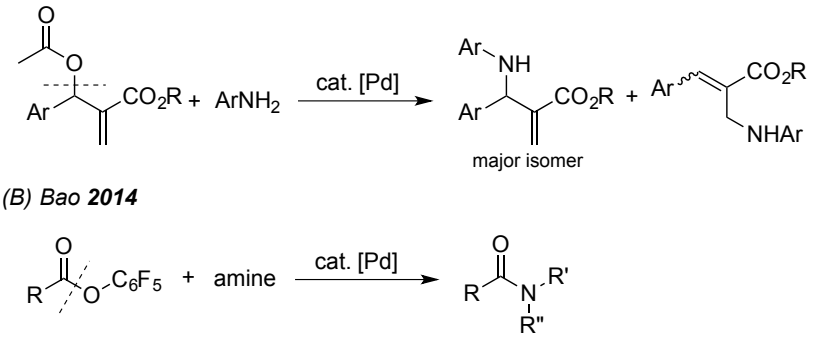
Murai and co-workers[49] reported a Ru-catalyzed acyl C-O bond activation of pyridine substituted esters (Scheme 58). In this reaction, the metallated ester intermediate undergoes decarbonylation to obtain arene products. Chatani and co-workers[50,51] extended Murai's work to a Pd-catalyzed cross-coupling reaction of similar substrates with aryl boronic acids to obtain unsymmetrical ketones. This reaction was limited to pyridine containing esters, in which the pyridine acts as a directing group to facilitate Pd-activation of the acyl C-O bond. To date, all examples of TM-catalyzed acyl C-O bond activation happen in the presence of directing groups or in activated esters.[52]



Scheme 58. Ru- and Pd-catalyzed acyl C-O bond activation of methylpyridine esters.

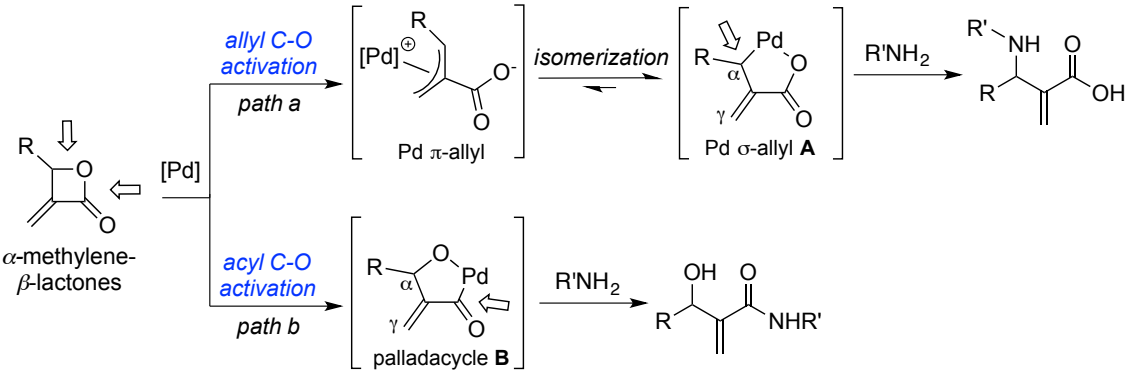
2.3.2 Mechanistic Hypothesis

Our interest in α-methylene-β-lactones as substrates in developing TM-catalyzed transformations led to us to evaluate their propensity to undergo selective ring-opening reactions. In particular, Ding and co-workers[53] recently reported the utility of MBH acetates in Pd-catalyzed allylic amination (Scheme 59A).[54,55] Analogous to Pd-catalyzed allylations, this reaction involves initial formation of a Pd-allyl intermediate formed from activation of an allyl C-O bond by palladium. Conversely, Bao[56] recently developed a Pd-catalyzed amidation of pentafluoroesters with various amines (Scheme 59B). This reaction was believed to involve an acyl C-O bond cleavage under palladium catalysis. However, instead of using substrates with pyridine directing groups, activated esters, such as those that possess good leaving groups (e.g. pentafluorophenyl) were utilized.



Scheme 59. Pd-catalyzed (A) allylic amination of acetates of MBH adducts and (B) aminolysis of aryl esters.

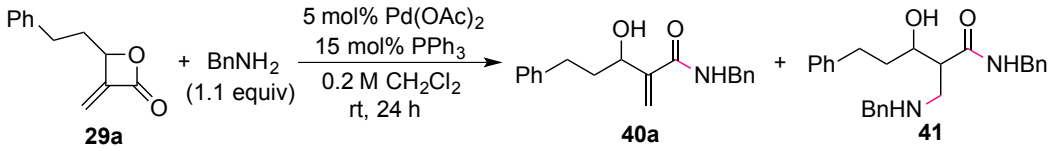
Based on these recent reports, we hypothesized that α-methylene-β-lactones could undergo a Pd-catalyzed selective ring-opening reaction with amines (Scheme 60). First, α-methylene-β-lactones might undergo oxidative addition to Pd(0) selectively, either via allylic C-O bond cleavage (path *a*) or olefin directed acyl C-O bond cleavage (path *b*). The resulting palladacyles (**A**[57] or **B**) could undergo ring-opening with amines to form either β-amino acids or β-hydroxy amides.



Scheme 60. Mechanistic hypothesis for Pd-catalyzed activation of α-methylene-β-lactones.

2.3.3 Results and Discussions

The initial exploration was conducted using α-methylene-β-lactone **29a** and reacting it with benzyl amine under palladium catalysis (Table 7, entry 1). No β-amino acid product was observed. Rather, α-methylene-β-hydroxy amide **40a** was isolated as the major product in 80% yield, and diaminated adduct **41** was observed as a minor product. The formation of **41** was believed to come from Michael addition of **40a** with excess benzyl amine.



Entry	Variation from standard condition[b]	Ratio **3:4**[c]	Yield **3**
1	2 equiv of $BnNH_2$, 0.5 M	4:1	80%
2	none	>20:1	92%
3	0 mol% $Pd(OAc)_2$	-	<5% conv[c]
4	0 mol% PPh_3	-	<10% conv[c]
5	45 °C, 12 h (instead of rt, 24 h)	>20:1	98%
6	2 mol% $[Pd(allyl)Cl]_2$; 6 mol% PPh_3	>20:1	90[d]
7	2 mol% $Pd_2(dba)_3$; 6 mol% PPh_3	>20:1	95[d]
8	5 mol% $Pd_2(dba)_3$; 0 mol% PPh_3	-	n. r.[e]
9	5 mol% $Pd(PPh_3)_4$; 0 mol% PPh_3	10:1	-

[a]Standard conditions: 0.1 to 0.2 mmol **29a**, 1.1 equiv benzylamine, 5 mol%$Pd(OAc)_2$, 15 mol% PPh_3, in 0.2 M CH_2Cl_2 at room temp for 24 h. Yiels are isolated yields. [b]Parameters varied from the standard conditions. [c]Ratio and conversions were estimated by ^1H NMR analysis of the crude reaction mixture. [d]^1H NMR yields using 1,3,5-trimethoxybenzene as internal standard. [e]No reaction, Pd black formation observed.

Table 7. Initial studies on the Pd-catalyzed reaction of α-methylene-β-lactone **29a** with benzylamine.

Various optimizations were conducted, and it was found that the desired β-hydroxy amide was obtained as the sole product in 92% yield when benzyl amine was used at 1.1 equivalents (Table 7, entry 2). Under these conditions typical conversions after 24h was ~95%. When the reaction was conducted at 45 °C, complete conversion was obtained with

quantitative yield (entry 5). Other palladium sources were also examined, and in most cases, similar results were obtained.

The nature of the active palladium catalyst is important. For example, when no phosphine ligand was used (Table 7, entries 4 and 8 or Figure 16, red line), no significant conversion (0 to <10%) was observed. This suggests that the active catalyst is a low valent palladium species, most likely Pd(0), as evidenced by the observed reactivity when a Pd(0) precursor $Pd(PPh_3)_4$ was used (entry 9). For the case of $Pd_2(dba)_3$ (entry 8), no reaction was observed mainly due to the decomposition of the Pd complex that formed (Pd black was deposited on the walls of the reaction tube). However, when $Pd_2(dba)_3$ was combined with the biphosphine ligand, BINAP, complete conversion was observed (Figure 16, purple line). It also worth mentioning that no reaction was observed when no palladium catalyst was used (Figure 16, light blue and blue lines).

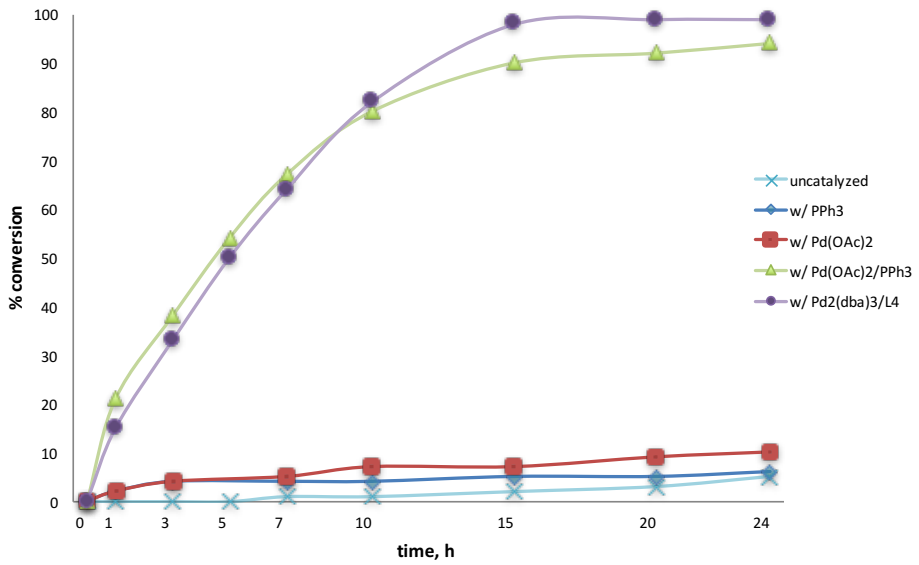
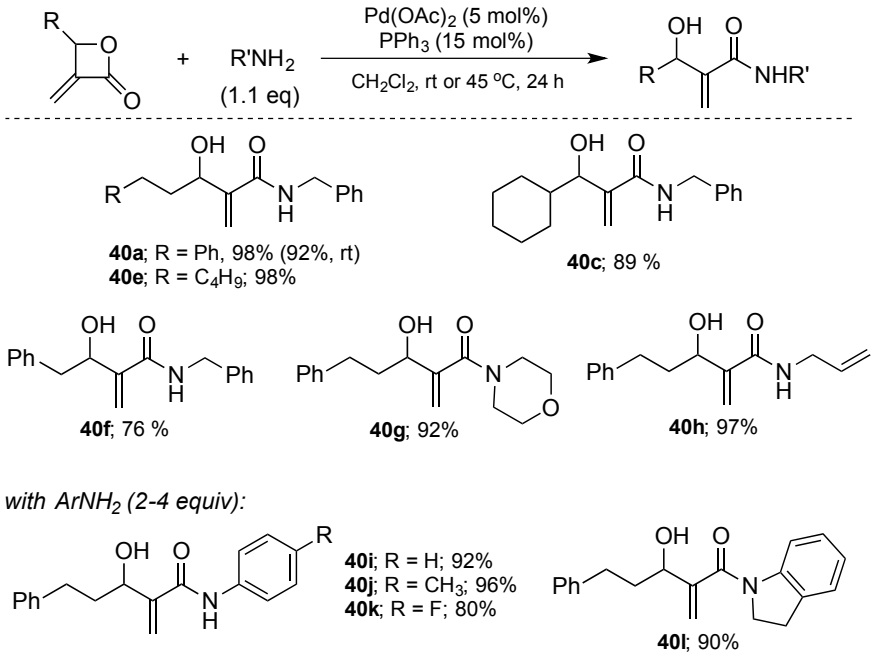


Figure 16. Reaction profile of lactone **29a** with benzyl amine under various conditions. Reaction conditions: 0.1 mmol **29a**, 0.11 mmol benzyl amine, in CD_2Cl_2 at rt. Percent conversions were obtained by ^1H NMR analysis of the reaction mixture using 1,3,5-trimethoxybenzene as internal standard; L4 = BINAP.

The observed selective ring-opening reaction of α-methylene-β-lactone to form an amide is remarkable in comparison to the results obtained by Ding when MBH acetates were

used (Scheme 58A). Likewise, typically, α-methylene-β-lactones react with nucleophiles, including secondary alkyl amines, via 1,4-addition (see Scheme 48).

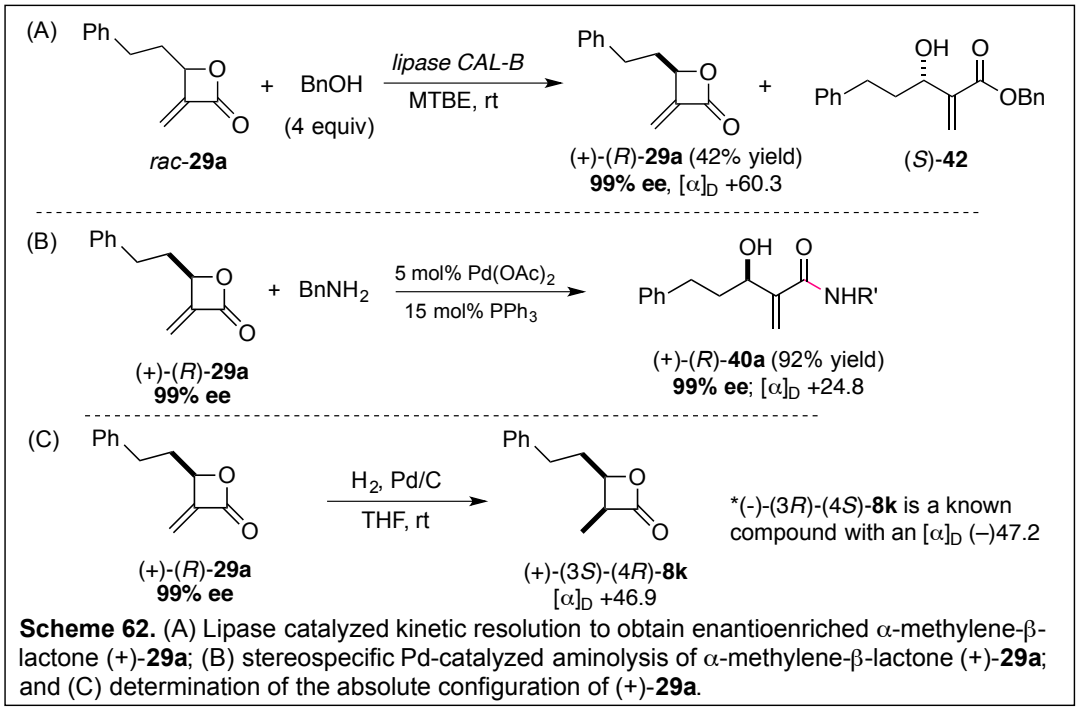


Scheme 61. Scope of the Pd-catalyzed amination of methylene-β-lactones with various types of amines.

Various alkyl amines (primary and secondary) gave β-hydroxy amides in excellent yields, all with complete chemoselectivity towards amidation products (Scheme 60). Likewise, less nucleophilic aryl amines were found effective for the selective ring-opening of α-methylene-β-lactones to form aryl amides. Both electron rich and deficient aryl amines coupled with α-methylene-β-lactones. The heterocycle, indoline, also coupled to form the indoline amide **40l**. In these reactions, 2 to 4 equivalents of aryl amines, reaction temperature of 45 °C and 0.5 M solutions (conc. of **29** in DCM) were necessary to obtain high conversions. Highly electron deficient aryl amines, such 2-nitroaniline and 4-nitroaniline, were found unreactive even after prolonged heating.

A highly enantioenriched β-lactone was accessed via enzymatic kinetic resolution of the racemic lactone **29a** (Scheme 61A). The kinetic resolution was done based from a

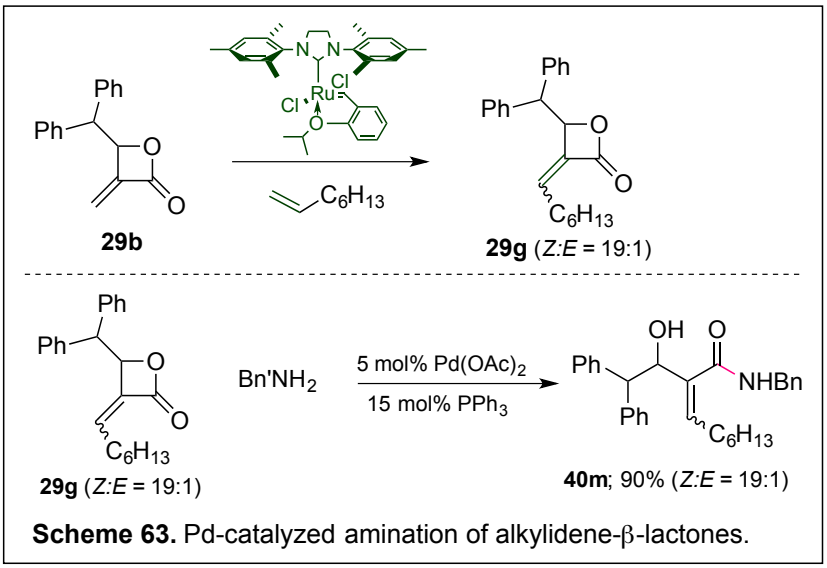
modified procedure originally developed by Adam and co-workers.[10] Reacting *rac*-**29a** with benzyl alcohol in the presence of lipase *CAL-B (Candida antarctica; Novozyme 435)* resulted in ~50% conversion after 24 h. α-Methylene-β-lactone (+)-**29a** was isolated in 42% yield. The absolute configuration of (+)-**29a** was determined by converting to (+)-**8k** through hydrogenation. The resulting product (+)-**8k** has an opposite configuration to know (–)-(3*R*)-(4*S*)-**8k**.[58] With this, the obtained (+)-**29a** was designated as the (*R*) isomer. HPLC analysis on a chiral column gave 99% ee for (*R*)-**29a**. Pd-catalyzed amidation of α-methylene-β-lactone (*R*)-**29a** gave chiral β-hydroxy amide (*R*)-**40a** in high yields without erosion of stereochemical integrity (Scheme 61B).



Scheme 62. (A) Lipase catalyzed kinetic resolution to obtain enantioenriched α-methylene-β-lactone (+)-**29a**; (B) stereospecific Pd-catalyzed aminolysis of α-methylene-β-lactone (+)-**29a**; and (C) determination of the absolute configuration of (+)-**29a**.

To further expand the scope of the reaction, an α-allkylidene-β-lactone was prepared using our previously reported protocol of Ru-catalyzed cross metathesis of α-methylene-β-lactones with olefins.[6] α-Allkylidene-β-lactone **29g** was treated with benzyl amine under palladium catalysis. α-Alkylidene-β-hydroxy amide **40m** was obtained in high yield and with

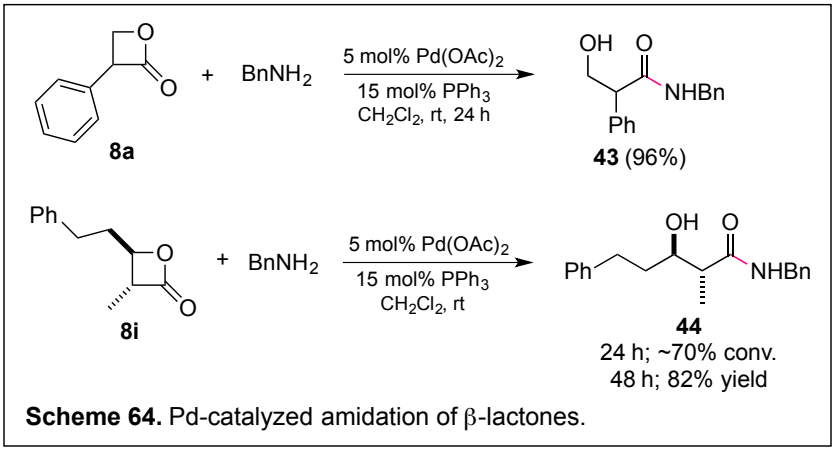
complete retention of olefin geometry. This type of product is difficult to access or unattainable via MBH reaction or CM of MBH adducts.



Scheme 63. Pd-catalyzed amination of alkylidene-β-lactones.

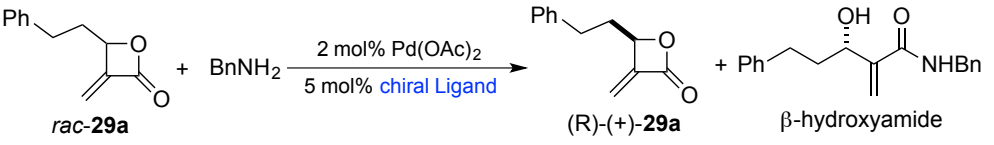
Analogous to previous reports on TM-catalyzed acyl C-O bond activation of esters,[50,51] a mechanism involving an olefin-mediated oxidative addition of Pd(0) to the acyl C-O bond of lactone to form a palladacycle intermediate is proposed (Scheme 59, path *b*). Coupling with amines[56] would provide the β-hydroxy amide products.

To extend the generality of this present method, simple β-lactones were treated under the same conditions. It is not surprising that α-phenyl-β-lactone **8a** underwent facile ring-opening with benzyl amine at rt. Similar to α-methylene-β-lactones, the aryl group facilitated the palladium towards acyl C–O bond activation. β-Lactone **8i** also furnished the corresponding amide product with complete selectivity, albeit in lower conversions. Nonetheless, when the reaction is done in a longer period of time, high yields can be obtained.

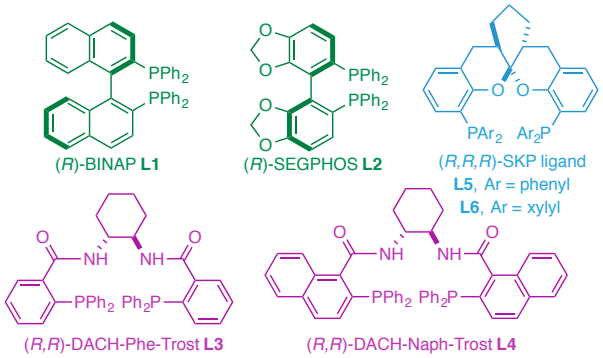


Scheme 64. Pd-catalyzed amidation of β-lactones.

To date, enantioenriched α-methylene-β-lactones were only accessed via kinetic resolution with enzymes.[10] Our interest in α-methylene-β-lactones as priviledged intermediates in organic synthesis led us to propose that the Pd-catalyzed amidation described above can be rendered stereoselective through kinetic resolution. Several chiral phosphine ligands typically used in Pd-catalyzed asymmetric allylic amination reactions were screened (Table 8). Racemic α-methylene-β-lactone **29a** underwent amidation reaction in all examples. Reactions were monitored by ^{1}H NMR analysis and were quenched after obtaining ~50-55% conversion. Ligands, such as homochiral BINAP and SEGPHOS did not provide any enantiomeric excess for either the amide or the unreacted **29a**. When Trost ligands (**L3** and **L4**) were utilized, enantiomeric excess of up to 38% was observed for the unreacted **29a**. To our delight, the spiroketal phosphine ligands developed by Ding and co-workers[53a] provided enantiomeric excess up to 68% for **L5**. The use of aniline, anisidine or benzyl alcohol (instead of benzyl amine) at room temperature gave no conversion. Reactions conducted at higher dilution (0.1 M in $CDCl_3$, instead of 0.2 M) or 0.5 equivalents of benzylamine gave very slow reaction, typically <10 conversion after 48 h.



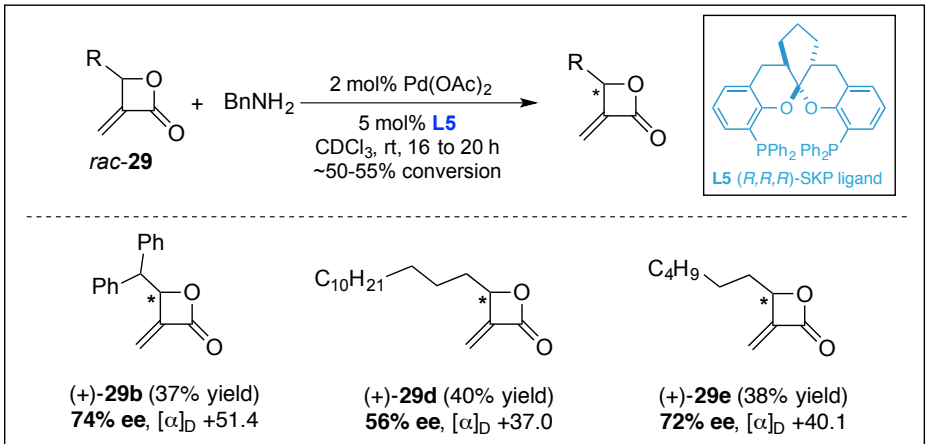
Ligand	(+)-β-lactone Yield	% ee
L1	40%	0
L2	trace (>90% conv, 12h)	0
L3	38%	5 (*R*)
L4	42%	38 (*R*)
L5	43%	68 (*R*)
L6	46%	40 (*R*)



Reaction conditions: 1 equiv $BnNH_2$, 0.2 M $CDCl_3$, rt, 16 - 20 h, >50-55% conversion

Table 8. Ligand screening for the asymmetric kinetic resolution of α-methylene-β-lactone.

The developed Pd-catalyzed asymmetric kinetic resolution was tested for several α-methylene-β-lactones (Scheme 65). Lactones **29b**, **29d** and **29e** were enantioenriched with modest enantiomeric excess up to 74%. Although this method suffers from loss in yield (50% maximum), it has the potential to be used as a late-stage enantiomeric enrichment of α-methylene-β-lactones.



(+)-**29b** (37% yield)
74% ee, $[\alpha]_D$ +51.4

(+)-**29d** (40% yield)
56% ee, $[\alpha]_D$ +37.0

(+)-**29e** (38% yield)
72% ee, $[\alpha]_D$ +40.1

Scheme 65. Pd-catalyzed asymmetric kinetic resolution of racemic α-methylene-β-lactones.

2.4 Conclusions

α-Methylene-β-lactones are a privileged class of lactones because of their ability to undergo a diverse range of useful reactions. Our previous work on Ru-catalyzed cross metathesis/reduction sequence to access disubstituted β-lactones with promising biological activities served as our benchmark to develop other transition metal catalyzed transformations of this important class of lactone. Two successful transformations were described above. The Rh-catalyzed conjugate addition with aryl boronic acids provided a one-step, highly efficient method to disubstituted β-lactones. The second transformation demonstated a highly selective ring-opening of β-lactones through amidation that involved acyl C-O bond activation by palladium.

2.5 Experimental

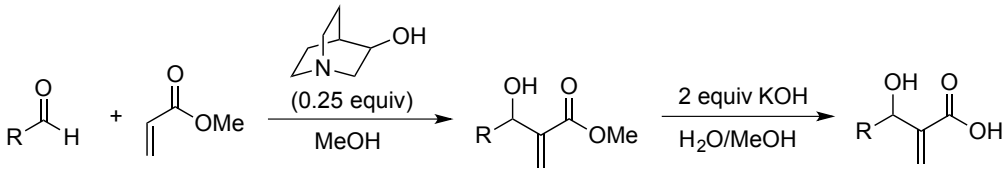
2.5.1 General Information

All moisture sensitive reactions were run in a flame-dried flask under N_2. Tetrahydrofuran (THF) was dried using J. C. Meyer Solvent Dispensing System (SDS) and dispensed under N_2. All other solvents were dried over CaH_2 or 4 Å molecular sieves. Deuterated chloroform ($CDCl_3$), and methylene chloride (CD_2Cl_2) were dried over 4 Å molecular sieves. Commercially available reagents were purchased from Aldrich, Acros, Alfa Aesar or TCI America and used without further purification.

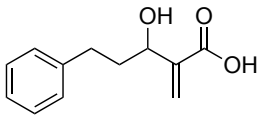
All ^1H NMR experiments were recorded using a Bruker AVANCE 300, 400 or 500 MHz spectrometer. All ^{13}C NMR experiments were recorded using a Bruker AVANCE 75, 100 or 125 MHz spectrometer. Chemical shifts (δ) are given in ppm, and coupling constants (*J*) are given in Hz. The 7.26 resonance of residual $CHCl_3$ for proton spectra and the 77.23 ppm resonance of $CDCl_3$ for carbon spectra were used as internal references. High-resolution mass spectra (HRMS) were obtained using DART AccuTOF or JEOL JMS-AX505HA mass spectrometers. Reaction progress was monitored by ^1H NMR analysis and/or by thin layer chromatography (TLC) performed on glass plates coated with silica gel UV254. Visualization was achieved by ultraviolet light (254 nm), 0.5% $KMnO_4$ in 0.1 M aqueous NaOH solution and/or 5% phosphomolybdic acid in ethanol. Column chromatography was performed using silica gel, 40 microns flash silica.

2.5.2 Preparation of α-methylene-β-hydroxyacids

General procedure for the preparation of α-methylene-β-hydroxyacids



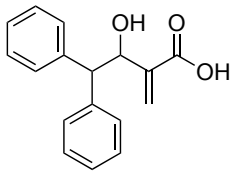
Methylacrylate (2 equiv) was added to a solution of aldehyde (1 equiv), MeOH (0.75 equiv), and quinuclidinol (0.25 equiv), and the mixture was stirred at rt. The reaction progress was monitored by ^{1}H NMR over a period of 2-3 days until >95% conversion. The reaction mixture was concentrated *in vacuo* to remove MeOH and excess methylacrylate. Aqueous 2.0 M NaOH (2 equiv) was added dropwise to the resulting crude mixture dissolved in MeOH (half the volume of NaOH solution). This was stirred for 2 days or until complete saponification. The progress of the reaction was monitored by ^{1}H NMR analysis or TLC. The reaction mixture was concentrated *in vacuo* to remove MeOH. The resulting aqueous solution was acidified using 10% aqueous HCl until pH 1 to 2. This was extracted with Et_2O (same volume as aqueous solution) three times. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.



37a

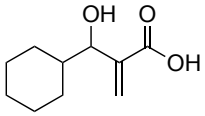
3-Hydroxy-2-methylene-5-phenylpentanoic acid (37a). The general procedure was followed using hydrocinnamaldehyde (4.00 g, 30.0 mmol), and the reaction mixture was stirred for 2 days. ^{1}H NMR analysis of the crude reaction mixture showed 95% conversion. Hydrolysis was done in 2 days. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 70:30) gave **37a** as a white solid (3.65 g, 59% over 2-steps):[34] ^{1}H NMR (300

MHz, $CDCl_3$) δ 7.33–7.18 (m, 5H), 6.43 (s, 1H), 5.95 (s, 1H), 4.47 (dd, *J* = 7.4, 5.5 Hz, 1H), 2.89-2.67 (m, 2H), 2.09–1.98 (m, 2H).



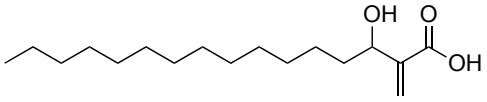
37b

3-Hydroxy-2-methylene-4,4-diphenylbutyric acid (37b). The general procedure was followed using diphenylacetaldehyde (2.94 g, 15.0 mmol), and the reaction mixture was stirred for 2 days. ^{1}H NMR analysis of the crude reaction mixture showed >95% conversion. Hydrolysis was done in 2 days. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 75:25) gave **37b** as a white foam (3.30 g, 83% over 2-steps):[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 10H), 6.29 (s, 1H), 5.71 (s, 1H), 5.23 (d, *J* = 8.0 Hz, 1H), 4.38 (d, *J* = 8.0 Hz, 1H).



37c

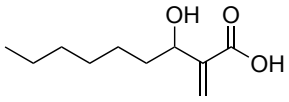
3-Cyclohexyl-3-hydroxy-2-methylenepropanoic acid (37c). The general procedure was followed using cyclohexanecarboxaldehyde (1.30 g, 11.6 mmol), and the reaction mixture was stirred for 2 days. ^{1}H NMR analysis of the crude reaction mixture showed >95% conversion. Hydrolysis was done in 2 days. Compound **37c** was obtained as a crude oil and carried to the next step with no further purification:[59] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (s, 1H) 5.83 (s, 1H) 4.11 (d *J* = 7.1 Hz, 1H) 1.97–1.93 (m, 1H) 1.75–1.56 (m, 6H) 1.24–0.96 (m, 4H).



37d

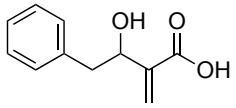
3-Hydroxy-2-methylenehexadecanoic acid (37d). The general procedure was followed using tetradecanal (2.98 g, 15.0 mmol), and the reaction mixture was stirred for 2 days. ^{1}H

NMR analysis of the crude reaction mixture showed about 100% conversion. Hydrolysis was done in 2 days. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 85:15) gave **37d** as a white solid (3.20 g, 75% over 2-steps):[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (s, 1H), 5.91 (s, 1H), 4.43 (dd, *J* = 6.5, 6.5 Hz, 1H), 1.68−1.66 (m, 2H), 1.43−1.41 (m, 1H), 1.30−1.26 (m, 22H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 142.1, 127.6, 71.8, 36.4, 32.1, 29.9, 29.9, 29.9, 29.8, 29.8, 29.6, 29.6, 26.0, 22.9, 14.3.



37e

3-Hydroxy-2-methylenenonanoic acid (37e). The general procedure was followed using heptaldehyde (3.40 g, 30.0 mmol), and the reaction mixture was stirred for 2 days. ^{1}H NMR analysis of the crude reaction mixture showed about 100% conversion. Hydrolysis was done in 2 days. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 80:20) gave compound **37e** as a white solid (2.50 g, 50% over 2-steps):[59] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (s, 1H), 5.91 (s, 1H), 4.42 (t, *J* = 7.2 Hz, 1H), 1.75–1.60 (m, 2H) ,1.51–1.20 (m, 8H), 0.95–0.81 (m, 3H).

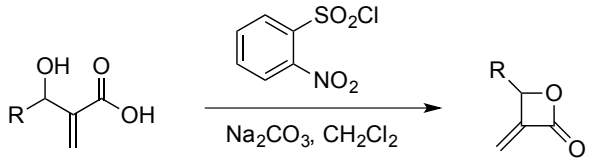


37f

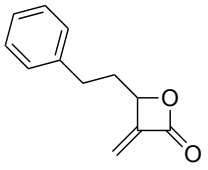
3-Hydroxy-2-methylene-4-phenylbutanoic acid (37f). The general procedure was followed using phenyl acetaldehyde (2.28 g, 19.0 mmol), and the reaction mixture was stirred for 3 h. ^{1}H NMR analysis of the crude reaction mixture showed about 100% conversion with other byproducts. Hydrolysis was completed in 1 day. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 80:20) gave **37f** as a thick yellowish oil (0.90 g, 23%):[60] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.19 (m, 5H), 6.41 (s, 1H), 5.94 (s, 1H), 4.45 (s, 1H) ,2.69 (m, 3H).

2.5.3 Preparation of α-methylene-β-lactones

General procedure for the preparation of α-methylene-β-lactones

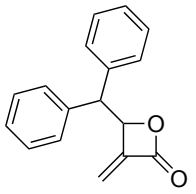


Na_2CO_3 (10 equiv) was added to α-methylene-β-hydroxyacid (1 equiv) in DCM (5 volumes; 5 mL DCM/mmol of limiting reagent), and the reaction mixture was stirred at rt. After 30 min, *o*-nosyl chloride (2 equiv) was added, and the resulting suspension was stirred at rt for 2 days or until complete conversion. The progress of the reaction was monitored by TLC or ^{1}H NMR analysis. The reaction mixture was with diluted with DCM (10 volumes) and H_2O (5 volumes) and stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with DCM (3 x 5 volumes). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification was done by flash chromatography on silica gel.



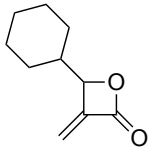
29a

4-(2-Phenylethyl)-3-methyleneoxetan-2-one (29a). The general procedure was followed using 3-hydroxy-2-methylene-5-phenylpentanoic acid (**37a**) (2.90 g, 14.1 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc 95:5) provided **29a** as a colorless oil (1.70 g, 65%):[34] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (m, 2H), 7.27–7.22 (m, 3H), 5.86 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.33 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.97 (dddd, *J* = 6.4, 6.4, 1.7, 1.7 Hz, 1H), 2.87–2.71 (m, 2H), 2.19–2.12 (m, 2H).



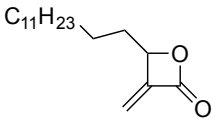
29b

4-Benzhydryl-3-methyleneoxetan-2-one (29b). The general procedure was followed using 3-hydroxy-2-methylene-4,4-diphenylbutyric acid (**37b**) (1.4 g, 5.2 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc 95:5) provided **29b** as a white solid (0.95 g, 73%):[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.23 (m, 10H), 5.74 (dd, *J* = 2.0, 1.4 Hz, 1H), 5.53 (ddd, *J* = 9.6, 2.0, 1.4 Hz, 1H), 4.72 (dd, *J* = 2.0, 1.4 Hz, 1H), 4.20 (d, *J* = 9.6, 1H).



29c

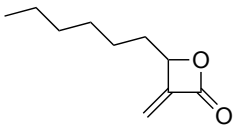
4-Cyclohexyl-3-methyleneoxetan-2-one (29c). The general procedure was followed using 3-cyclohexyl-3-hydroxy-2-methylenepropanoic acid (**37c**) (1.40 g, 5.20 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc 95:5) provided **29c** as a colorless oil (0.67 g, 77%):[59] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 1.7, 1.7 Hz, 1H), 5.42 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.69 (ddd, *J* = 7.1, 1.7, 1.7 Hz, 1H), 1.87–1.10 (m, 11H).



29d

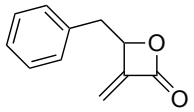
3-Methylene-4-tridecyloxetan-2-one (29d). The general procedure was followed using 3-hydroxy-2-methylenehexadecanoic acid (**37d**) (2.50 g, 9.25 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc 98:2) provided **29d** as a colorless oil (1.60 g, 65%):[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 1.9, 1.9 Hz, 1H), 5.39 (dd, *J* = 1.7,

1.7 Hz, 1H), 4.92 (dddd, *J* = 6.5, 6.5, 1.6, 1.6 Hz, 1H), 1.81 (dddd, *J* = 7.1, 7.1, 7.1, 0.0 Hz, 1H), 1.81 (dddd, *J* = 7.8, 7.8, 7.8, 0.0 Hz, 1H), 1.46–1.40 (m, 2H), 1.33–1.22 (m, 20H), 0.84 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 146.6, 114.8, 79.7, 33.4, 32.0, 29.8, 29.7, 29.7, 29.6, 29.5, 29.5, 29.3.



29e

4-Hexyl-3-methyleneoxetan-2-one (29e). The general procedure was followed using 3-hydroxy-2-methylenenonanoic acid (**37e**) (2.90 g, 14.1 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc 94:4) provided **29e** as a colorless oil (1.85 g, 78%): IR (neat): 2955, 2929, 2859, 1813, 1206, 1077 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.39 (dd, *J* = 1.6, 1.6 Hz, 1H), 4.92 (dddd, *J* = 6.6, 6.6, 1.8, 1.8 Hz, 1H), 1.80 (ddd, *J* = 7.4, 7.4, 7.4 Hz, 2H), 1.46–1.37 (m, 2H), 1.33–1.24 (m, 6H), 0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 146.5, 114.9, 79.7, 33.4, 31.6, 29.0, 24.6, 22.5, 14.1; HRMS (ESI) calcd for $C_{10}H_{17}O_2$ $(M + H)^+$ *m/z* 169.1229, found 169.1217.

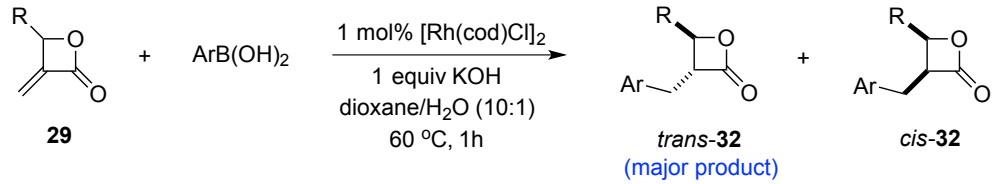


29f

4-Benzyl-3-methyleneoxetan-2-one (29f). The general procedure was followed using 3-hydroxy-2-methylene-4-phenylbutanoic acid (**37f**) (900 mg, 4.68 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc 94:4) provided **29f** as a pale yellow oil (244 mg, 30%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 5H), 5.89 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.23 (dd, *J* = 1.6, 1.6 Hz, 1H), 5.14 (dddd, *J* = 6.8, 6.8, 1.6, 1.6 Hz, 1H), 3.29 (dd, *J* = 14.1, 6.8 Hz, 1H), 3.05 (dd, *J* = 14.1, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 145.8, 134.8, 129.5, 128.9, 127.5, 116.2, 79.0, 39.7; HRMS (ESI) calcd for $C_{11}H_{10}O_2$ $(M + H)^+$ *m/z* 175.0759, found 175.0742.

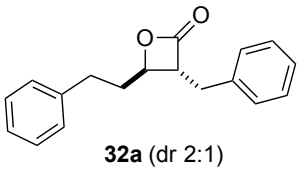
2.4.4 Rh-catalyzed conjugate addition of aryl boronic acids to α-methylene-β-lactones

General procedure for the Rh-catalyzed conjugate addition of α-methylene-β-lactones with aryl boronic acids



Aryl boronic acid (1.5 equiv, 0.75 mmol) and 1 mol% $[Rh(cod)Cl]_2$ (0.05 mmol, 3.0 mg) were placed in a reaction tube equipped with a stir bar. The reaction tube was capped with a rubber septum then filled and back-filled with N_2 three times. Aqueous 2 M KOH solution (1 equiv, 0.25 mL) was added, followed by the α-methylene-β-lactone **29** dissolved in dioxane (2.5 mL). The resulting yellow solution was stirred in an oil bath at 60 °C for 1 h. An aliquout of the reaction mixture was analyzed by ^{1}H NMR to determine the diastereoselectivity. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography. In all cases, the *trans* isomers were obtained as the major products.

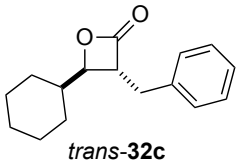
For inseparable mixture of isomeric products, the major product (*trans* isomer) is drawn. Diastereomeric ratios (dr) were obtained from ^{1}H NMR analyses of the crude mixture.



32a (dr 2:1)

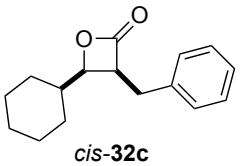
***trans*/*cis*-3-Benzyl-4-(2-phenylethyl)oxetan-2-one (32a).** The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one **29a** (94 mg, 0.50 mmol) and phenyl boronic acid (92 mg, 0.75 mmol). Purification by column chromatography on silica gel (hexanes/EtOAc 99:1) provided **32a** as a colorless oil (122 mg, 92%; *trans:cis* 2:1):[14a] ^{1}H NMR

for *trans*-**32a** (400 MHz, $CDCl_3$) δ 7.37-7.11 (m, 10H), 4.32 (ddd, *J* = 10.0, 6.0, 4.1 Hz, 1H), 3.52 (ddd, *J* = 9.9, 5.9, 4.0 Hz, 1H), 3.14 (dd, *J* = 14.0, 5.9 Hz, 1H), 2.99 (dd, *J* = 14.3, 9.0 Hz, 1H), 2.27–2.62 (m, 1H), 2.55–2.48 (m, 1H), 2.21–2.12 (m, 1H), 2.01–1.94 (m, 1H); ^1H NMR for *cis*-**32a** (400 MHz, $CDCl_3$) δ 7.37–7.11 (m, 10H), 4.64 (ddd, *J* = 10.0, 6.4, 3.2 Hz, 1H), 4.04 (ddd, *J* = 8.9, 6.9, 6.9 Hz, 1H), 3.22 (dd, *J* = 14.9, 7.1 Hz, 1H), 2.99 (dd, *J* = 14.3, 9.0 Hz, 1H), 2.94–2.89 (m, 1H), 2.72–2.62 (m, 1H), 2.21–2.12 (m, 1H), 2.01–1.94 (m, 1H).



trans-**32c**

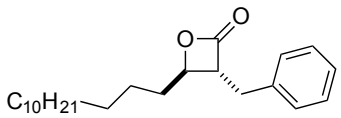
***trans*-3-Benzyl-4-cyclohexyloxetan-2-one (*trans*-32c).** The general procedure was followed using 4-cyclohexyl-3-methyleneoxetan-2-one (**29c**) (83 mg, 0.50 mmol) and phenyl boronic acid (92 mg, 0.75 mmol). Purification by column chromatography on silica gel (hexanes/EtOAc 94:6) provided *trans*-**32c** as a colorless oil (73 mg, 60%): IR (neat) 2925, 2853, 1814, 1389, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.30 (m, 2H), 7.27–7.23 (m, 1H), 7.20–7.19 (m, 2H), 3.97 (dd, *J* = 8.6, 4.1 Hz, 1H), 3.49 (ddd, *J* = 9.8, 5.9, 4.1 Hz, 1H), 3.15 (dd, *J* = 14.1, 5.9 Hz, 1H), 2.97 (dd, *J* = 14.1, 8.9 Hz, 1H), 1.86–1.79 (m, 1H), 1.73–1.55 (m, 4H) 1.34–0.64 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 137.4, 129.1, 129.0, 127.3, 81.3, 56.0, 41.8, 34.4, 28.6, 27.0, 26.1, 25.5, 25.3; HRMS (ESI) calcd for $C_{16}H_{21}O_2$ $(M + H)^+$ *m/z* 245.1542, found 245.1540.



cis-**32c**

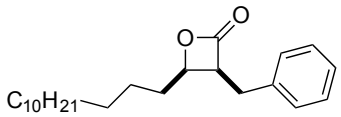
***cis*-3-Benzyl-4-cyclohexyloxetan-2-one (*cis*-32c).** *cis*-3-Benzyl-4-cyclohexyloxetan-2-one (*cis*-**32c**) was obtained as the minor isomer from the above reaction. Compound *cis*-**32c** was obtained as a colorless oil (37 mg, 30%): IR (neat): 2926, 2852, 1814, 1452, 1132 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$) δ 7.34–7.30 (m, 2H), 7.27–7.24 (m, 3H), 4.25 (dd, *J* = 10.2, 6.2 Hz, 1H), 3.98 (ddd, *J* = 8.6, 6.9, 6.9 Hz, 1H), 3.19 (dd, *J* = 14.8, 8.7 Hz, 1H), 3.05 (dd, *J* = 14.8, 7.0 Hz, 1H), 2.00–1.96 (m, 1H), 1.83–1.68 (m, 4H) 1.49–0.88 (m, 6H); HRMS (ESI) calcd for $C_{16}H_{21}O_2$ $(M + H)^+$ *m/z* 245.1542, found 245.1539.



trans-**32e**

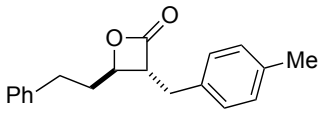
***trans*-3-Benzyl-4-tridecyloxetan-2-one (*trans*-32e).** The general procedure was followed using 3-methylene-4-tridecyloxetan-2-one (**29d**) (130 mg, 0.50 mmol) and phenyl boronic acid (92 mg, 0.75 mmol). Purification by column chromatography on silica gel (hexanes/EtOAc 99:1) provided *trans*-**32a** as a white solid (103 mg, 60%):[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.30 (m, 2H), 7.27−7.25 (m, 2H), 7.20 (m, 1H), 4.27 (ddd, *J* = 6.7, 6.7, 4.1 Hz, 1H), 3.45 (m, 1H), 3.18 (dd, *J* = 14.3, 5.7 Hz, 1H), 3.00 (dd, *J* = 14.3, 9.4 Hz, 1H), 1.83−1.74 (m, 1H), 1.62−1.57 (m, 1H), 1.35−1.18 (m, 22H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 137.4, 129.1, 128.9, 127.3, 77.8, 57.6, 34.4, 34.0, 32.1, 29.9, 29.9, 29.8, 29.6, 29.6, 29.6, 29.3, 24.8, 22.9, 14.3.



cis-**32e**

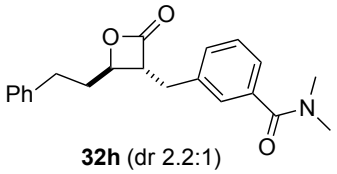
***cis*-3-Benzyl-4-tridecyloxetan-2-one (*cis*-32e).** *cis*-3-Benzyl-4-tridecyloxetan-2-one (*cis*-**32e**) was isolated as the minor isomer from the above reaction. Compound *cis*-**32e** was obtained as a colorless oil (43 mg, 25%):[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.30 (m, 2H), 7.24−7.21 (m, 3H), 4.60 (ddd, *J* = 10.0, 6.4, 3.6 Hz, 1H), 4.01 (ddd, *J* = 9.0, 6.9, 6.9 Hz, 1H), 3.19 (dd, *J* = 15.1, 7.1 Hz, 1H), 2.98 (dd, *J* = 15.1, 9.0 Hz, 1H), 1.86−1.76 (m, 1H), 1.71−1.63 (m, 1H), 1.57−1.46 (m, 1H), 1.37−1.26 (m, 21H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 171.7, 137.9, 129.0, 128.6, 127.0, 76.3, 53.5, 32.1, 30.6, 29.9, 29.9, 29.8, 29.7, 29.6, 29.6, 29.5, 25.8, 22.9, 14.3.



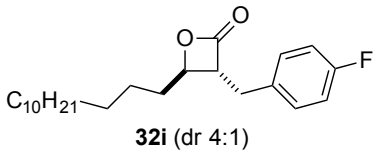
32g (dr 2:1)

***trans*/*cis*-3-(4-Methyl)benzyl-4-(2-phenylethyl)oxetan-2-one (32g).** The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**29a**) (94.mg, 0.50 mmol) and tolyl boronic acid (100 mg, 0.75 mmol). Purification by column chromatography on silica gel (hexanes/EtOAc 96:4) provided **32g** (*trans:cis* = 2:1) as a colorless oil (122 mg, 87%; dr 2:1): IR (neat) 3026, 2923, 1815, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for the major isomer *trans*-**32g** δ 7.35–7.05 (m, 9H), 4.30 (ddd, *J* = 7.4, 5.9, 4.1 Hz, 1H), 3.49 (ddd, *J* = 9.0, 6.0, 4.1 Hz, 1H), 3.07 (dd, *J* = 14.4, 6.0 Hz, 1H), 2.94 (dd, *J* = 14.3, 8.8 Hz, 1H), 2.73–2.62 (m, 1H), 2.56–2.49 (m, 1H), 2.35 (s, 3H), 2.21–2.10 (m, 1H), 2.04–1.92 (m, 1H); for the minor isomer *cis*-**32g** δ 7.35–7.05 (m, 9H), 4.61 (ddd, *J* = 10.0, 6.4, 3.2 Hz, 1H), 4.00 (ddd, *J* = 9.0, 7.0, 7.0 Hz, 1H), 3.16 (dd, *J* = 15.0, 7.2 Hz, 1H), 2.94 (m, 1H), 2.91–2.87 (m, 1H), 2.73–2.63 (m, 1H), 2.35 (s, 3H), 2.21–2.10 (m, 1H), 2.04–1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major isomer *trans*-**32g** δ 170.8, 140.3, 136.8, 134.0, 129.7, 128.7, 128.7, 128.4, 126.5, 76.7, 57.6, 35.8, 33.3, 31.1; for the minor isomer *cis*-**32g** δ 171.4, 140.5, 136.6, 134.5, 129.6, 128.8, 128.7, 128.3, 126.5, 75.0, 53.5, 32.3, 31.7, 29.4; HRMS (ESI) calcd for $C_{19}H_{21}O_2$ $(M + H)^+$ *m/z* 281.1542, found 281.1546.



32h (dr 2.2:1)

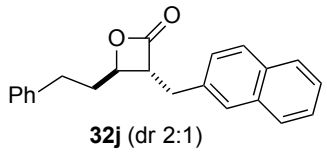
***trans/cis*-3-[3-(*N,N*-Dimethylbenzamide)]methyl-4-(2-phenylethyl)oxetan-2-one (32h).** The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**29a**) (94 mg, 0.50 mmol) and benzamide-3-boronic acid (145 mg, 0.75 mmol). Purification by column chromatography on silica gel (hexanes/EtOAc 85:15) provided **32h** as a white solid (118 mg, 70%; dr 2.2:1; isolated product contains ~2% Heck coupling product: mp 40–41 ^{o}C; IR (neat) 3010, 2931, 1818, 1625, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for the major isomer *trans*-**32h** δ 7.35–7.10 (m, 9H), 4.27 (m 1H), 3.48 (m, 1H), 3.19–2.84 (m, 2H), 3.09 (s, 3H), 2.92 (s, 3H), 2.71–2.64 (m, 1H), 2.57–2.50 (m, 1H), 2.18–2.08 (m, 1H), 2.01–1.91 (m, 1H); for the minor isomer *cis*-**32h** δ 7.35–7.10 (m, 9H), 4.60 (ddd, *J* = 9.9, 6.3, 3.1 Hz, 1H), 3.98 (m, 1H), 3.19–2.84 (m, 3H), 3.09 (s, 3H), 2.92 (s, 3H), 2.71–2.64 (m, 1H), 2.18–2.08 (m, 1H), 2.01–1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) as a mixture of *trans/cis*-**32g** δ 171.3, 171.2, 171.1, 170.4, 140.3, 140.1, 137.8, 137.3, 137.1, 137.0, 130.0, 129.6, 129.0, 128.9, 128.8, 128.6, 128.4, 127.6, 127.1, 126.5, 125.9, 125.7, 76.4, 74.8 (minor) , 57.1, 53.1 (minor), 39.6 (br), 35.8, 35.4, 33.4 (br), 32.4, 31.7, 31.2, 29.7, 29.7 (selected, underlined peaks are major peaks relative to those labeled minor peaks); HRMS (ESI) calcd for $C_{21}H_{24}NO_3$ $(M + H)^+$ *m/z* 338.1756, found 338.1772.



32i (dr 4:1)

***trans*/*cis*-3-(4-Fluoro)benzyl-4-tridecyloxetan-2-one (32i).** The general procedure was followed using 3-methylene-4-tridecyloxetan-2-one (**29d**) (130 mg, 0.50 mmol) and 4-fluorophenyl boronic acid (150 mg, 0.75 mmol). Purification by column chromatography on silica gel (hexanes/EtOAc 98:2) provided trans/cis-**32i** as a white solid (170 mg, 92%; *trans:cis*

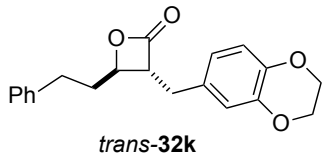
= 4:1): IR (neat) 2923, 2853, 1820, 1510, 1224 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for the major isomer *trans*-**32i**: δ 7.21–7.15 (m, 2H), 7.03-7.0 (m, 2H), 4.25 (ddd, *J* = 6.7, 6.7, 4.1 Hz, 1H), 3.42 (ddd, *J* = 8.9, 6.0, 4.1 Hz, 1H), 3.13 (dd, *J* = 14.4, 6.1 Hz, 1H), 2.99 (dd, *J* = 14.3, 8.9, 1H), 1.84-1.77 (m, 1H), 1.64–1.57 (m, 1H), 1.32–1.20 (m, 22H), 0.88 (t, *J* = 6.6 Hz, 3H); for *the minor isomer cis*-**32i**: δ 7.21–7.15 (m, 2H), 7.03–7.0 (m, 2H), 4.60 (ddd, J = 10.0, 6.4, 3.6 Hz, 1H), 3.94 (ddd, *J* = 8.0, 8.0, 6.4 Hz, 1H), 3.17–3.10 (m, 1H), 3.97–2.91 (m,1 H), 1.84–1.77 (m, 1H), 1.64–1.57 (m, 1H), 1.32–1.20 (m, 22H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major isomer *trans*-**32i** δ 170.8, 162.1 (d, J_{C-F} = 245.9 Hz), 133.0 (d, J_{C-F} = 3.1 Hz), 130.4 (d, J_{C-F} = 8.0 Hz), 116.0 (d, J_{C-F} = 21.5 Hz), 77.5, 34.4, 33.2, 32.1, 29.9, 29.8, 29.8, 29.6, 29.6, 29.3, 24.9, 22.9, 14.3; for the minor isomer *cis*-**32i** δ 171.4, 162.0 (d, J_{C-F} = 245.2 Hz), 133.5 (d, J_{C-F} = 2.9 Hz), 130.1 (d, J_{C-F} = 8.1 Hz), 115.8 (d, J_{C-F} = 21.5 Hz), 76.0, 34.4, 32.1, 30.6, 29.9, 29.8, 29.7, 29.6, 29.5, 29.2, 27.8, 22.9, 14.3; HRMS (ESI) calcd for $C_{23}H_{36}FO_2$ $(M + H)^+$ *m/z* 363.2699, found 363.2684.



32j (dr 2:1)

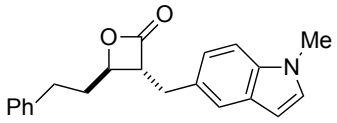
***trans*/*cis*-3-(2-Naphthyl)methyl-4-(2-phenylethyl)oxetan-2-one (32j).** The general procedure was followed using 3-methylene-4-phenethyloxetan-2-one (**29a**) (130 mg, 0.50 mmol) and naphthyl-2-boronic acid (130 mg, 0.75 mmol). Purification by column chromatography on silica gel (hexanes/EtOAc 95:5) provided *trans/cis*-**32j** as a colorless thick oil (170 mg, 84%; *trans:cis* = 2:1): IR (neat) 3058, 3026, 2927, 2859, 1813, 1119, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for the major isomer *trans*-**32j** δ 7.84–7.78 (m, 3H), 7.58 (s, 1H), 7.52–7.02 (m, 8H), 4.34 (ddd, *J* = 7.6, 5.8, 4.1 Hz, 1H), 3.58 (ddd, *J* = 9.1, 5.9, 4.1 Hz, 1H), 3.27 (dd, *J* = 14.3, 5.9 Hz, 1H), 3.13 (dd, *J* = 14.3, 9.0 Hz, 1H), 2.65–2.58 (m, 1H), 2.54–2.47 (m, 1H), 2.21–2.09 (m, 1H), 2.06–1.90 (m, 1H); for the minor isomer *cis*-**32j** δ 7.84–7.78 (m,

3H), 7.62 (s, 1H), 7.52–7.02 (m, 8H), 4.65 (ddd, *J* = 9.8, 6.3, 3.1 Hz, 1H), 4.13 (ddd, *J* = 9.0, 6.8, 6.8 Hz, 1H), 3.35 (dd, *J* = 15.2, 7.1 Hz, 1H), 3.13 (dd, *J* = 15.1, 9.0, 1H), 2.90 (ddd, *J* = 14.0, 9.3, 4.7 Hz, 1H), 2.72–2.65 (m, 1H), 2.21–2.09 (m, 1H), 2.06–1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major isomer *trans*-**32j** δ 170.7, 140.2, 134.6, 133.7, 132.6, 128.9–126.0 (multiple overlapping arene carbon peaks), 76.8, 57.5, 35.8, 34.0, 31.2; for the minor isomer *cis*-**32j** δ 171.4, 140.4, 135.1, 133.7, 132.5, 128.9–126.0 (multiple overlapping arene carbon peaks), 75.1, 53.4, 32.3, 31.7, 30.1; HRMS (ESI) calcd for $C_{22}H_{21}O_2$ $(M + H)^+$ *m/z* 317.1542, found 317.1555.



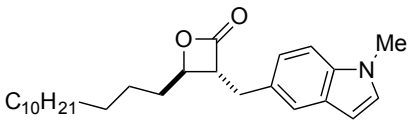
trans-**32k**

***trans*-3-[6-(1,4-Benzodioxanyl)]methyl-4-(2-phenylethyl)oxetan-2-one (*trans*-32k).** The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**29a**) (94 mg, 0.50 mmol) 1,4-benzodioxan-6-boronic acid (140 mg, 0.75 mmol). Purification by column chromatography on silica gel (hexanes/EtOAc 85:15) provided *trans*-**32k** as a colorless oil (97 mg, 60%; combined yield 92%): IR (neat) 2924, 2872, 1816, 1508, 1260 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.27 (m, 2H), 7.23–7.19 (m, 1H), 7.11 (d, *J* = 7.1 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 2.1 Hz, 1H), 6.60 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.28 (ddd, *J* = 7.4, 5.9, 4.1 Hz, 1H), 4.24 (s, 4H), 3.43 (ddd, *J* = 9.1, 5.9, 4.1 Hz, 1H), 2.98 (dd, *J* = 14.3, 5.9 Hz, 1H), 2.85 (dd, *J* = 14.4, 9.0 Hz, 1H), 2.66 (ddd, *J* = 14.5, 9.6, 5.3 Hz, 1H), 2.52 (ddd, 14.2, 9.2, 7.0 Hz, 1H), 2.13 (dddd, *J* = 16.7, 9.0, 7.3, 5.5 Hz, 1H), 1.96 (dddd, *J* = 15.5, 9.5, 6.7, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 143.9, 142.8, 140.3, 130.3, 128.8, 128.5, 126.6, 121.7, 117.8, 117.6, 76.8, 64.6, 64.5, 57.7, 36.0, 33.1, 31.2; HRMS (ESI) calcd for $C_{20}H_{21}O_4$ $(M + H)^+$ *m/z* 325.1440, found 325.1422.



trans-**32l**

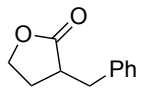
***trans*-3-(5-*N*-Methylindolyl)methyl-4-(2-phenylethyl)oxetan-2-one (*trans*-32l).** The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**29a**) (94 mg, 0.50 mmol) and *N*-methyl-5-indolylboronic acid (131 mg, 0.75 mmol). Purification by column chromatography on silica gel (hexanes/EtOAc 90:10) provided *trans*-**32l** as a light pink solid (104 mg, 65%; combined yield 90%): mp 96–98 ^{o}C; IR (neat) 2924, 1816, 1508, 1260 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 0.9 Hz, 1H), 7.28–7.24 (m, 3H), 7.21-7.18 (m, 1H), 7.06–6.99 (m, 3H), 7.00 (dd, *J* = 3.0, 0.5 Hz, 1H), 6.43 (dd, *J* = 3.1, 0.6 Hz, 1H), 4.34 (ddd, *J* = 7.5, 5.8, 4.1 Hz, 1H), 3.79 (s, 3H), 3.54 (ddd, *J* = 9.3, 5.6, 4.0 Hz, 1H), 3.21 (dd, *J* = 14.3, 5.7 Hz, 1H), 3.07 (dd, *J* = 14.4, 9.2 Hz, 1H), 2.59 (ddd, *J* = 14.3, 9.6, 5.7 Hz, 1H), 2.47 (ddd, *J* = 14.1, 9.2, 6.9 Hz, 1H), 2.10 (dddd, *J* = 16.8, 9.1, 7.4, 5.7 Hz, 1H), 1.92 (dddd, *J* = 15.6, 9.6, 6.6, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 140.4, 136.1, 129.6, 129.0, 128.7, 128.5, 127.9, 126.4, 122.4, 120.9, 109.8, 100.9, 76.9, 58.3, 36.0, 33.9, 33.1, 31.2; HRMS (ESI) calcd for $C_{21}H_{22}NO_2$ $(M + H)^+$ *m/z* 320.1651, found 320.1652.



trans-**32m**

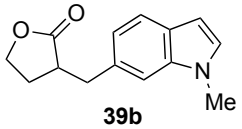
***trans*-3-(5-*N*-Methylindolyl)methyl-4-tridecyloxetan-2-one (*trans*-32m).** The general procedure was followed using 3-methylene-4-tridecyloxetan-2-one (**29d**) (130 mg, 0.50 mmol) and *N*-methyl-5-indolylboronic acid (131 mg, 0.75 mmol). Purification by column chromatography on silica gel (hexanes/EtOAc 90:10) provided *trans*-**32m** as a light pink oil (130 mg, 67%; combined yield 75%): IR (neat) 3021, 2924, 2853, 1816, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 0.9 Hz, 1H), 7.287 (d, *J* = 8.1 Hz, 1H), 7.05–7.03 (m, 2H), 6.43 (dd, *J* = 3.0, 0.5 Hz, 1H), 4.32 (ddd, *J* = 6.6, 6.6, 4.1 Hz, 1H), 3.78 (s, 3H), 3.50 (ddd, *J*

= 9.3, 5.5, 4.1 Hz, 1H), 3.25 (dd, *J* = 14.3, 5.5 Hz, 1H), 3.10 (dd, *J* = 14.3, 9.3 Hz, 1H), 1.78–1.13 (m, 24H) 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 136.1, 129.6, 129.4, 128.1, 122.5, 77.8, 58.2, 34.4, 34.1, 33.1, 32.1, 29.9, 29.9, 29.8, 29.8, 29.6, 29.6, 29.3, 24.9, 22.9, 14.3; HRMS (ESI) calcd for $C_{26}H_{40}NO_2$ $(M + H)^+$ *m/z* 398.3059, found 398.3048.



39a

3-Benzyltetrahydrofuran-2-one (39a). The general procedure was followed using 3-methylenebutyrolactone (**38**) (49 mg, 0.50 mmol) and phenyl boronic acid (92 mg, 0.75 mmol). Purification by column chromatography on silica gel (hexanes/EtOAc 92:8) provided **39a** as a colorless oil (160 mg, 93%):[61] ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.16 (m, 2H), 7.12–7.07 (m, 3H), 4.05 (ddd, *J* = 8.8, 8.8, 3.0 Hz, 1H), 3.97 (ddd, *J* = 9.4, 9.4, 6.7 Hz, 1H), 3.09 (dd, *J* = 13.5, 3.9 Hz, 1H), 2.70 (ddd, *J* = 13.5, 9.2, 4.2 Hz, 1H), 2.61 (dd, *J* = 13.5, 9.3 Hz, 1H), 2.12−2.04 (m, 1H), 1.88−1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 138.4, 128.8, 128.5, 126.6, 66.4, 40.9, 35.9, 27.8.



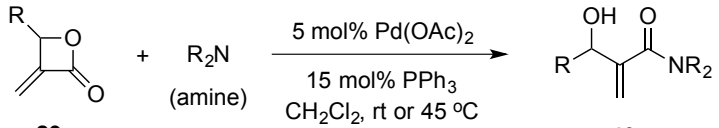
39b

3-(6-*N*-Methylindolyl)methyltetrahydrofuran-2-one (39b). The general procedure was followed using 3-methylenebutyrolactone (**38**) (49 mg, 0.50 mmol) and *N*-methyl-5-indolylboronic acid (130 mg, 0.75 mmol). Purification by column chromatography on silica gel (hexanes/EtOAc 85:15) provided **39b** as a light pink solid (102 mg, 89%): mp 52–53 °C; IR (neat) 3013, 2912, 1759, 1150, 1020, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 1.1 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.07 (d, *J* = 3.1 Hz, 1H), 6.46 (dd, *J* = 3.1, 0.7 Hz, 1H), 4.16 (ddd, *J* = 9.0, 9.0, 3.4 Hz, 1H), 4.09 (ddd, *J* = 9.0, 9.0, 7.0 Hz, 1H), 3.78 (s, 3H), 3.38–3.32 (m, 1H), 2,91–2.83 (m, 2H), 2.23–2.15 (m, 1H), 2.07–1.96 (m,

1H); %): ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 135.8, 129.4, 129.1, 128.8, 122.6, 120.8, 109.5, 100.6, 66.7, 41.7, 36.2, 32.9, 27.9; HRMS (ESI) calcd for $C_{14}H_{16}NO_2$ $(M + H)^+$ *m/z* 230.1191, found 230.1191.

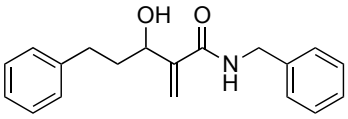
2.5.4 Pd-catalyzed amidation of α-methylene-β-lactones

General procedure for the Pd-catalyzed amidation of α-methylene-β-lactones with amines



29 **40**

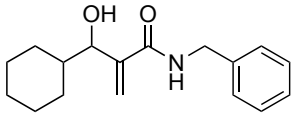
Anhydrous DCM (0.25 mL) was added to a reaction tube containing 5 mol% $Pd(OAc)_2$ (0.005 mmol, 1.1 mg) and 15 mol% PPh_3 (0.015 mmol, 4.0 mg) and stirred for 20 min at rt. The α-methylene-β-lactone (1.0 equiv, 0.1 mmol) in DCM (0.25 mL) was added via syringe, followed by the amine (1.1 equiv, 0.11 mmol; for aryl amines, 2-4 equiv. were used). The reaction mixture was stirred for 24 h at rt or 45 °C. The reaction mixture was filtered through a short pad of silica which was rinsed with DCM (2 x 2 mL). The crude mixture was concentrated *in vacuo* and purified by column chromatography on silica gel.



40a

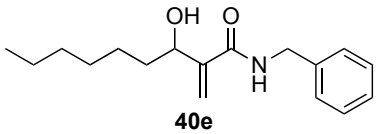
***N*-Benzyl-3-hydroxy-2-methylene-5-phenylpentanamide (40a).** The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**29a**) (19 mg, 0.10 mmol) and benzylamine (12 mg, 0.11 mmol), and the reaction was performed at 45 °C. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **40a** as a pale yellow solid (29 mg, 98%): mp 96–97 °C; IR (neat) 3307 (br), 3027, 2925, 2855, 1715, 1654, 1605, 1535, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.18 (m, 7H), 7.13–7.09 (m, 3H), 6.64 (br

s, 1H), 5.71 (s, 1H), 5.38 (s, 1H), 4.45 (dd, *J* = 14.8, 5.8 Hz, 1H), 4.41 (dd, *J* = 14.8, 5.7 Hz, 1H), 4.31 (dd, *J* = 7.9, 5.7 Hz, 1H), 3.08 (br s, 1H), 2.71 (ddd, *J* = 14.2, 9.6, 6.0 Hz, 1H), 2.59 (ddd, *J* = 15.9, 9.2, 6.7 Hz, 1H), 2.03–1.94 (m, 1H), 1.93–1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 145.7, 141.7, 138.2, 129.0, 128.7, 128.6, 128.0, 127.8, 126.2, 120.1, 73.4, 43.7, 37.5, 32.3; HRMS (ESI) calcd for $C_{19}H_{22}NO_2$ $(M + H)^+$ *m/z* 296.1651, found 296.1664.



40c

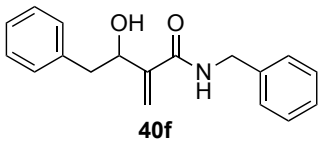
***N*-Benzyl-3-hydroxy-2-methylene-3-phenylpropanamide (40c).** The general procedure was followed using 4-cyclohexyl-3-methyleneoxetan-2-one (**29c**) (19 mg, 0.10 mmol) and benzylamine (12 mg, 0.11 mmol), and the reaction was performed at rt. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **40c** as a yellowish solid (24 mg, 89%): mp 82–83 °C; IR (neat) 3306 (br), 2923, 2851, 1654, 1609, 1537, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.31 (m, 2H), 7.28–7.26 (m, 3H), 7.00 (br s, 1H), 5.82 (s, 1H), 5.37 (s, 1H), 4.52 (dd, *J* = 14.9, 5.8 Hz, 1H), 4.48 (dd, *J* = 14.9, 5.8 Hz, 1H), 3.97 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.28 (d, *J* = 6.1 Hz, 1H), 2.04–2.01 (m, 1H), 1.76–1.50 (m, 5H), 1.23–1.13 (m, 3H), 0.99–0.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 144.5, 138.3, 128.9, 127.8, 127.7, 121.5, 80.0, 43.5, 42.2, 30.0, 29.5, 26.5, 26.1, 26.0; HRMS (ESI) calcd for $C_{17}H_{24}NO_2$ $(M + H)^+$ *m/z* 274.1807, found 274.1813.



40e

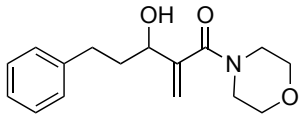
***N*-Benzyl-3-hydroxy-2-methylenenonanamide (40e).** The general procedure was followed using 4-hexyl-3-methyleneoxetan-2-one (**29e**) (17 mg, 0.10 mmol) and benzylamine (12 mg, 0.11 mmol), and the reaction was performed at rt. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **40e** as a white solid (27 mg, 98%): mp 77–78 °C;

IR (neat) 3389 (br), 2954, 2926, 2856, 1654, 1609, 1536, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 2H), 7.30–7.28 (m, 3H), 6.83 (br s, 1H), 5.80 (s, 1H), 5.45 (s, 1H), 4.52 (dd, *J* = 14.9, 5.7 Hz, 1H), 4.48 (dd, *J* = 14.9, 5.7 Hz, 1H), 4.36 (dd, *J* = 12.5, 6.2 Hz, 1H), 2.94 (d, *J* = 5.5 Hz, 1H), 1.71–1.60 (m, 2H), 1.40–1.27 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 145.8, 138.3, 129.0, 127.9, 127.8, 120.1, 74.3, 43.7, 36.0, 31.9, 29.3, 26.1, 22.8, 14.3; HRMS (ESI) calcd for $C_{17}H_{26}NO_2$ $(M + H)^+$ *m/z* 276.1964, found 276.1961.



40f

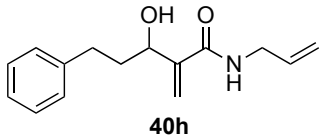
***N*-Benzyl-3-hydroxy-2-methylene-4-phenylbutanamide (40f).** The general procedure was followed using 4-benzyl-3-methyleneoxetan-2-one (**29f**) (18 mg, 0.10 mmol) and benzylamine (12 mg, 0.11 mmol), and the reaction was performed at rt. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **40f** as a pale yellow solid (21 mg, 76%): mp 102–104 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.16 (m, 10H), 6.72 (br s, 1H), 5.77 (s, 1H), 5.42 (s, 1H), 4.62 (dd, *J* = 5.7, 5.7 Hz, 1H), 4.53 (d, *J* = 5.7 Hz, 2H), 3.06–2.94 (m, 3H), 3.02 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 144.6, 138.2, 137.9, 129.6, 128.9, 128.6, 127.8, 127.6, 126.7, 120.8, 74.7, 43.5, 42.9; HRMS (ESI) calcd for $C_{18}H_{20}NO_2$ $(M + H)^+$ *m/z* 282.1494, found 282.1482.



40g

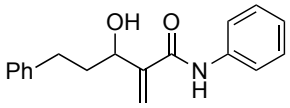
***N*-(3-Hydroxy-2-methylene-5-phenyl)pentanoylmorpholine (40g).** The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**29a**) (19 mg, 0.10 mmol) and morpholine (10 mg, 0.11 mmol), and the reaction was performed at rt. Purification by column chromatography on silica gel (hexanes/EtOAc 60:40) provided **40g** as a pale yellow oil (25 mg, 92%): IR (neat) 3386 (br), 2922, 2855, 1643, 1604, 1436, 1069, 700 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 7.31–7.26 (m, 3H), 7.21–7.19 (m, 2H), 5.50 (s, 1H), 5.18 (s, 1H), 4.32 (ddd, *J* = 12.9, 6.4, 6.4 Hz, 1H), 3.65 (br s, 8H), 3.05 (d, *J* = 6.3 Hz, 1H), 2.85 (ddd, *J* = 14.2, 7.6, 7.6 Hz, 1H), 2.71 (ddd, *J* = 14.4, 7.9, 7.9 Hz, 1H), 1.94–1.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 145.1, 141.7, 128.7, 128.7, 126.2, 116.4, 77.43, 73.2, 67.1, 37.8, 32.3; HRMS (ESI) calcd for $C_{16}H_{22}NO_3$ $(M + H)^+$ *m/z* 276.1600, found 276.1617.



40h

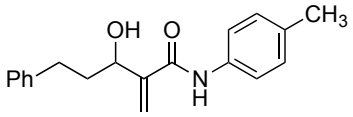
***N*-Allyl-3-hydroxy-2-methylene-5-phenylpentanamide (40h).** The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**29a**) (19 mg, 0.10 mmol) allylamine (6 mg, 0.11 mmol), and the reaction was performed at rt. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **40h** as a pale yellow solid (24 mg, 97%): mp 74–75 °C; IR (neat) 3306 (br), 2922, 2860, 1655, 1605, 1531, 921, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 3H), 7.20–7.17 (m, 2H), 6.53 (br s, 1H), 5.90–5.81 (m, 1H), 5.78 (s, 1H), 5.45 (s, 1H), 5.20 (dddd, *J* = 17.2, 1.6, 1.6, 1.6 Hz, 1H), 5.16 (dddd, *J* = 10.3, 1.4, 1.4, 1.4 Hz, 1H), 4.37 (ddd, *J* = 7.8, 5.8, 5.8 Hz, 1H), 3.95–3.92 (m, 2H), 3.23 (d, *J* = 6.0 Hz, 1H), 2.79 (ddd, *J* = 14.0, 5.9, 5.9 Hz, 1H), 2.68 (ddd, *J* = 14.1, 6.7, 6.7 Hz, 1H), 2.10–2.01 (m, 1H), 1.99–1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 145.7, 141.7, 134.0, 128.7, 128.6, 126.2, 120.0, 116.8, 73.4, 42.0, 37.5, 32.3; HRMS (ESI) calcd for $C_{15}H_{20}NO_2$ $(M + H)^+$ *m/z* 246.1494, found 246.1521.



40i

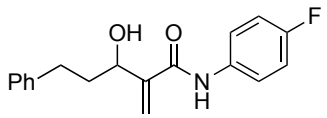
3-Hydroxy-2-methylene-*N*-phenyl-5-phenylpentanamide (40i). The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**29a**) (19 mg, 0.10 mmol) aniline (41 mg, 0.44 mmol), and the reaction was performed at 45 °C. Purification by column

chromatography on silica gel (hexanes/EtOAc 70:30) provided **40i** as a pale yellow solid (26 mg, 92%): mp 126–128 ^{o}C; IR (neat) 3306 (br), 3305, 2924, 2860, 1650, 1618, 1522, 747, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (br s, 1H), 7.57–7.55 (m, 2H), 7.36–7.26 (m, 4H), 7.21–7.11 (m, 4H), 6.01 (s, 1H), 5.54 (s, 1H), 4.48 (dd, *J* = 7.8, 7.8 Hz, 1H), 2.94 (br s, 1H), 2.84–2.76 (m, 1H), 2.75–2.68 (m, 1H), 2.18–2.08 (m, 1H), 2.07–1.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 145.6, 141.4, 137.8, 129.3, 128.7, 126.3, 124.8, 122.1, 120.4, 73.6, 37.3, 32.3; HRMS (ESI) calcd for $C_{18}H_{20}NO_2$ $(M + H)^+$ *m/z* 282.1494, found 282.1498.



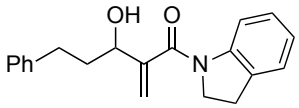
40j

3-Hydroxy-*N*-(4-methylphenyl)-2-methylene-5-phenylpentanamide (40j). The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**29a**) (19 mg, 0.10 mmol) toluidine (24 mg, 0.22 mmol), and the reaction was performed at 45 ^{o}C. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **40j** as a pale yellow solid (28 mg, 96%): mp 113–115 ^{o}C; IR (neat) 3286 (br), 3026, 2921, 2861, 1658, 1597, 1513, 813, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 7.44–7.42 (m, 2H), 7.30–7.26 (m, 2H), 7.21–7.17 (m, 3H), 7.14–7.12 (m, 2H), 5.98 (s, 1H), 5.50 (s, 1H), 4.45 (dd, *J* = 7.9, 5.8 Hz, 1H), 3.19 (br s, 1H), 2.83–2.67 (m, 2H), 2.32 (s, 3H), 2.16–2.07 (m, 1H), 2.05–1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 145.6, 141.4, 135.2, 134.5, 129.7, 128.7, 128.7, 126.2, 121.9, 120.5, 73.5, 37.4, 32.3, 21.1; HRMS (ESI) calcd for $C_{19}H_{22}NO_2$ $(M + H)^+$ *m/z* 296.1651, found 296.1681.



40k

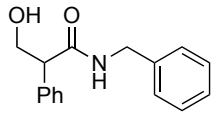
3-Hydroxy-*N*-(4-fluorophenyl)-2-methylene-5-phenylpentanamide (40k). The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**29a**) (19 mg, 0.10 mmol) and 4-fluoroaniline (50 mg, 0.44 mmol), and the reaction was performed at 45 °C. Purification by column chromatography on silica gel (hexanes/EtOAc 70:30) provided **40k** as a pale yellow solid (24 mg, 80%): mp 78–79 °C; IR (neat) 3293 (br), 2926, 2859, 1660, 1611, 1540, 1508, 832, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 7.54–7.49 (m, 2H), 7.31–7.26 (m, 2H), 7.21–7.18 (m, 3H), 7.04–6.99 (m, 2H), 6.03 (s, 1H), 5.52 (s, 1H), 4.47 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.05 (br s, 1H), 2.84–2.66 (m, 2H), 2.18–1.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 141.3, 139.7 (d, J_{C-F} = 653 Hz), 128.7, 128.7, 126.3, 122.2 (d, J_{C-F} = 8.3 Hz), 115.9 2 (d, J_{C-F} = 22.5 Hz), 73.5, 37.4, 32.3; HRMS (ESI) calcd for $C_{19}H_{19}FNO_2$ $(M + H)^+$ *m/z* 300.1400, found 300.1417.



40l

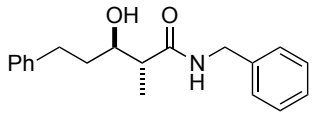
***N*-(3-hydroxy-2-methylene-5-phenyl)-pentanoylindoline (40l).** The general procedure was followed using 4-(2-phenylethyl)-3-methyleneoxetan-2-one (**29a**) (19 mg, 0.10 mmol) and indoline (52 mg, 0.44 mmol), and the reaction was performed at 45 °C. Purification by column chromatography on silica gel (hexanes/EtOAc 60:40) provided **40l** as a brownish thick oil (28 mg, 90%): IR (neat) 3404 (br), 2922, 1641, 1618, 1481, 1408, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (br s, 1H), 7.29–7.26 (m, 3H), 7.22–7.15 (m, 5H), 7.06 (dd, *J* = 7.4, 7.4 Hz, 1H), 5.62 (s, 1H), 5.42 (s, 1H), 4.44 (dd, *J* = 6.6, 6.6 Hz, 1H), 4.17–4.04 (m, 2H), 3.14 (dd, *J* = 14.9, 8.2 Hz, 1H), 3.07 (dd, *J* = 14.9, 8.2 Hz, 1H), 2.94–2.87 (m, 1H), 2.77–2.70 (m, 1H), 2.01 (dd, *J* = 7.7, 7.7 Hz, 1H), 1.99 (dd, *J* = 7.7, 7.7 Hz, 1H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ

168.9, 147.2, 142.4, 141.9, 132.6, 128.7, 128.6, 127.6, 126.1, 125.1, 124.6, 117.8, 116.9, 73.1, 50.8 (br), 38.0, 32.4, 28.3 (br); HRMS (ESI) calcd for $C_{20}H_{22}NO_2$ $(M + H)^+$ *m/z* 308.1651, found 308.1662.



43

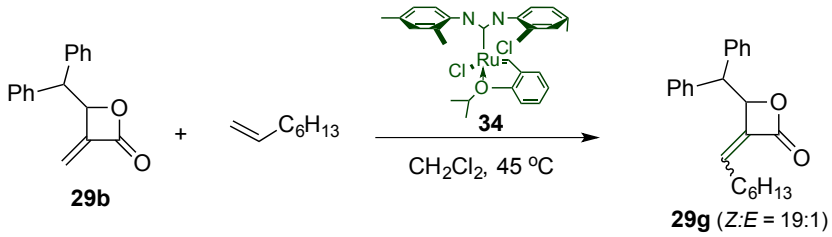
***N*-Benzyl-3-hydroxy-2-phenylpropanamide (43).** The general procedure was followed using 2-phenyloxetan-2-one (**8a**) (15 mg, 0.10 mmol) and benzyl amine (12 mg, 0.11 mmol), and the reaction was performed at rt. Purification by column chromatography on silica gel (hexanes/EtOAc 60:40) provided **43** as a white solid (25 mg, 96%): mp 116–118 ^oC; IR (neat) 3276 (br), 3030, 2924, 1638, 1548, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 8H), 7.18–7.16 (m, 2H), 5.82 (br s, 1H), 4.43 (dd, *J* = 14.9, 5.8 Hz, 1H), 4.43 (dd, *J* = 14.9, 5.8 Hz, 1H), 4.18 (dd, *J* = 11.0, 8.8 Hz, 1H), 3.80 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.70 (dd, *J* = 8.7, 4.5 Hz, 1H), 3.44 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 138.0, 136.8, 129.4, 128.9, 128.7, 128.2, 127.7, 127.7, 65.3, 54.6, 43.7; HRMS (ESI) calcd for $C_{16}H_{18}NO_2$ $(M + H)^+$ *m/z* 256.1338, found 256.1349.



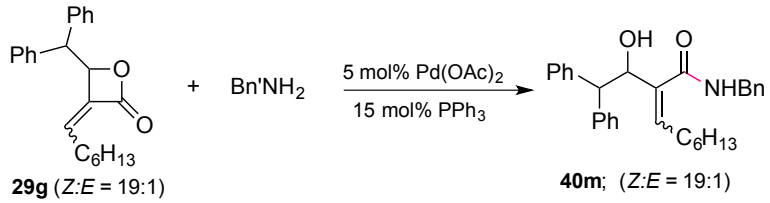
44

(*2R*,3R)-*N*-Benzyl-3-hydroxy-2-methyl-5-phenylpentanamide (44).** The general procedure was followed using *trans*-3-methyl-4-(2-phenylethyl)-oxetan-2-one (**8i**) (19 mg, 0.10 mmol) and benzyl amine (12 mg, 0.11 mmol), and the reaction was performed at rt for 48 h. Purification by column chromatography on silica gel (hexanes/EtOAc 60:40) provided **44** as a white solid (24 mg, 82%): mp 133–135 ^oC; IR (neat) 3293 (br), 2914, 1643, 1549, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.24 (m, 7H), 7.20–7.16 (m, 3H), 6.17 (br s, 1H), 4.43 (d, *J* = 2.5 Hz, 1H), 4.41 (d, *J* = 2.5 Hz, 1H), 3.63 (dddd, *J* = 5.4, 5.4, 5.4, 0.0 Hz, 1H), 3.40

(br s, 1H), 2.86 (ddd, *J* = 14.2, 7.4, 7.4 Hz, 1H), 2.67 (ddd, *J* = 13.9, 8.0, 8.0 Hz, 1H), 2.26 (dq, *J* = 7.1, 5.2 Hz, 1H), 1.82–1.76 (m, 2H), 1.26 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 142.2, 138.2, 128.9, 128.7, 128.6, 127.9, 127.8, 126.1, 73.5, 46.2, 43.5, 37.6, 32.4, 15.9; HRMS (ESI) calcd for $C_{19}H_{24}NO_2$ $(M + H)^+$ *m/z* 298.1807, found 298.1813.

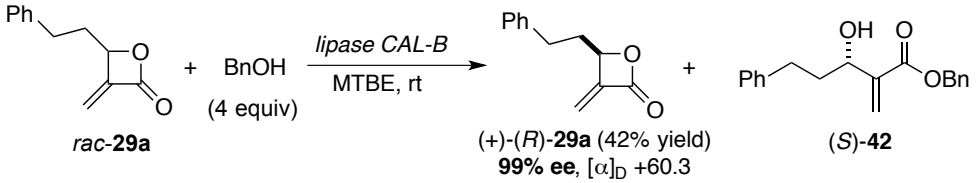


4-Benzhydryl-3-heptylideneoxetan-2-one (29g). 1-Octene (84 mg, 0.75 mmol) was added to a solution of 4-benzhydryl-3-methyleneoxetan-2-one **29b** (130 mg, 0.50 mmol equiv) under N_2 in DCM (2 mL). Catalyst **34** (5 mol%) was added, and the resultant solution was heated at reflux. The reaction was monitored by ^{1}H NMR. Upon consumption (~20 h) of **29b**, the solution was cooled and concentrated, and the brown residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 99:1). Lactone **29g** was obtained as a clear oil (114 mg, 68%, *Z/E* >19:1): ^{1}H NMR (400 MHz, $CDCl_3$) for the major isomer: δ 7.37–7.28 (m, 7H), 7.26–7.22 (m, 3H), 5.48 (d, *J* = 9.2 Hz, 1H), 5.18 (ddd, *J* = 8.1, 8.1, 1.0 Hz, 1H), 4.20 (d, *J* = 9.2 Hz, 1H), 2.45–2.30 (m, 2H), 1.33–1.21 (m, 8H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 140.0, 139.6, 139.0, 136.1, 129.0, 128.8, 128.5, 127.8, 127.3, 79.1, 55.1, 31.6, 29.2, 28.8, 28.7, 22.7, 14.2.



29g (*Z*:*E* = 19:1) **40m**; (*Z*:*E* = 19:1)

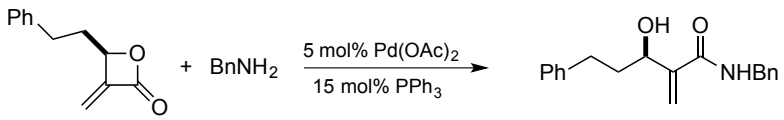
***N*-Benzyl-4,4-diphenyl-2-heptylidene-3-hydroxybutanamide (40m).** The general procedure for the Pd-catalyzed amidation was followed using 4-benzhydryl-3-heptylideneoxetan-2-one (**29g**) (34 mg, 0.10 mmol) and benzyl amine (12 mg, 0.11 mmol), and the reaction was performed at 45 °C. Purification by column chromatography on silica gel (hexanes/EtOAc 80:20) provided **40m** as a pale yellow oil (40 mg, 90%, *Z*/*E* 19:1): IR (neat) 3323 (br), 2954, 2926, 2856, 1660, 1601, 746, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for the major isomer: δ 7.37–7.28 (m, 9H), 7.22–7.08 (m, 6H), 5.93 (dd, *J* = 5.3, 5.3 Hz, 1H), 5.30 (dd, *J* = 10.4, 7.6 Hz, 1H), 4.89 (dd, *J* = 10.0, 5.4 Hz, 1H), 4.49 (dd, *J* = 14.6, 5.9 Hz, 1H), 4.45 (dd, *J* = 14.6, 5.9 Hz, 1H), 4.16 (d, *J* = 10.0 Hz, 1H), 3.09 (d, *J* = 5.4 Hz, 1H), 2.09–2.04 (m, 2H), 1.26–1.00 (m, 8H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 142.0, 141.5, 138.3, 138.1, 135.8, 129.0, 128.9, 128.8, 128.8, 128.6, 128.3, 127.9, 127.0, 126.8, 78.9, 57.4, 43.6, 31.8, 29.3, 29.3, 28.9, 22.7, 14.3; HRMS (ESI) calcd for $C_{30}H_{36}NO_2$ $(M + H)^+$ *m/z* 442.2746, found 442.2770.



rac-**29a** (+)-(*R*)-**29a** (42% yield) **99% ee**, $[\alpha]_D$ +60.3 (*S*)-**42**

(*4R*)-4-(2-Phenylethyl)-3-methyleneoxetan-2-one [(*R*)-29a]. Lipase CAL-B (lipase acrylic resin from *Candida Antarctica;* 19 mg) was added to a solution of 4-(2-phenylethyl)-3-methyleneoxetan-2-one (*rac*-**29a**) (190 mg, 1.0 mmol) and benzyl alcohol (4 mmol) in MTBE (5 mL). The resulting suspension was stirred at rt, and conversion was monitored by ^1H NMR. After 24 h, ~50% conversion was obtained. Percent conversion was estimated based from the

ratio of unreacted **29a** and **42**. The reaction mixture was passed through a pad of Celite and washed with MTBE (3 x 5 mL). The filtrate was dried (Na_2SO_4) and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel (hexanes/EtOAc 95:5) and gave (*R*)-**29a** as a colorless oil (79 mg, 42%):[34] $[\alpha]^{20}_D$ = (+)-60.3 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (m, 2H), 7.27–7.22 (m, 3H), 5.86 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.33 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.97 (dddd, *J* = 6.4, 6.4, 1.7, 1.7 Hz, 1H), 2.87–2.71 (m, 2H), 2.19–2.12 (m, 2H); 99% ee, retention time 7.7 min (major) and 8.7 min (minor) on Chiralpak AY3 (5% IPA/hexane, 1.0 mL/min).



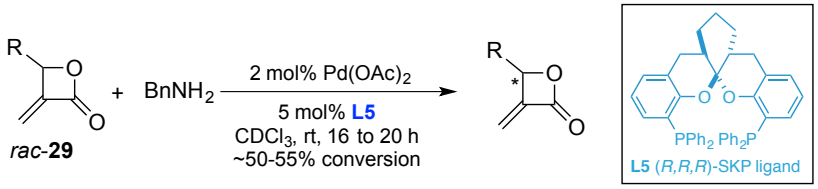
(+)-(*R*)-**29a**
99% ee

(+)-(*R*)-**40a** (92% yield)
99% ee; $[\alpha]_D$ +24.8

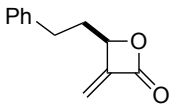
(3*R*)-*N*-Benzyl-3-hydroxy-2-methylene-5-phenylpentanamide [(*R*)-40a]. Anhydrous DCM (0.25 mL) was added to a reaction tube containing 5 mol% $Pd(OAc)_2$ (0.005 mmol, 1.1 mg) and 15 mol% PPh_3 (0.015 mmol, 4.0 mg), and the solution was stirred for 20 min at rt. (*R*)-4-(2-Phenylethyl)-3-methyleneoxetan-2-one [(*R*)-**29a**] (19 mg, 0.1 mmol) in DCM (0.25 mL) was added via syringe, followed by the benzyl amine (12 mg, 0.11 mmol). The reaction mixture was stirred for 24 h 45 °C. The reaction mixture was filtered through a short pad of silica which was rinsed with DCM (2 x 2 mL). The crude mixture was concentrated *in vacuo* and purified by column chromatography on silica gel (hexanes/EtOAc 70:30) and gave (*R*)-**40a** as a pale yellow solid (27 mg, 92%): $[\alpha]^{20}_D$ = (+)-24.8 (*c* = 1.00, $CHCl_3$); mp 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.18 (m, 7H), 7.13–7.09 (m, 3H), 6.64 (br s, 1H), 5.71 (s, 1H), 5.38 (s, 1H), 4.45 (dd, *J* = 14.8, 5.8 Hz, 1H), 4.41 (dd, *J* = 14.8, 5.7 Hz, 1H), 4.31 (dd, *J* = 7.9, 5.7 Hz, 1H), 3.08 (br s, 1H), 2.71 (ddd, *J* = 14.2, 9.6, 6.0 Hz, 1H), 2.59 (ddd, *J* = 15.9, 9.2, 6.7 Hz,

1H), 2.03–1.94 (m, 1H), 1.93–1.84 (m, 1H); 99% ee, retention time 12.2 min (major) and 13.2 min (minor) on Chiralcel OJ (2% IPA/hexane, 1.5 mL/min).

General procedure for the Pd-catalyzed kinetic resolution of α-methylene-β-lactones with benzylamine.

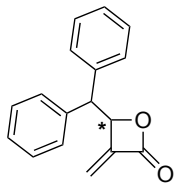


Deuterated chloroform (0.50 mL) was added to a reaction tube containing 2 mol% $Pd(OAc)_2$ (0.004 mmol, 1.0 mg) and 5 mol% **L5** (0.010 mmol, 6.6 mg), and the solution was stirred for 20 min at rt. The α-methylene-β-lactone (1.0 equiv, 0.2 mmol) in $CDCl_3$ (0.50 mL) was added via syringe, followed by the amine (1.0 equiv, 0.2 mmol). The reaction mixture was stirred at rt for 16 to 20 h until 50–55% conversion was reached. The reaction was monitored by ^1H NMR analysis. The reaction mixture was filtered through a short pad of silica which was rinsed with DCM (2 x 2 mL). The crude mixture was concentrated *in vacuo* and purified by column chromatography on silica gel.



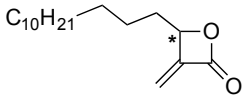
(R)-(+)-**29a**

(4*R*)-4-(2-Phenylethyl)-3-methyleneoxetan-2-one ([*R*]-[+]-29a). The general procedure was followed using racemic **29a** (38 mg, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc 95:5) provided (*R*)-(+)-**29a** as a colorless oil (16 mg, 43%):[34] $[\alpha]^{20}_D$ = (+)-40.3 (*c* = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (m, 2H), 7.27–7.22 (m, 3H), 5.86 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.33 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.97 (dddd, *J* = 6.4, 6.4, 1.7, 1.7 Hz, 1H), 2.87–2.71 (m, 2H), 2.19–2.12 (m, 2H); 68% ee, retention time 7.7 min (major) and 8.7 min (minor) on Chiralpak AY3 (5% IPA/hexane, 1.0 mL/min).



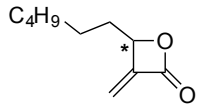
(+)-**29b**

4-Benzhydryl-3-methyleneoxetan-2-one ([+]-29b). The general procedure was followed using racemic **29b** (0.2 mmol, 50 mg). Purification by column chromatography on silica gel (petroleum ether/EtOAc 95:5) provided (+)-**29b** as a white solid (19 mg, 37%):[6] $[\alpha]^{20}_{D}$ = (+)-51.4 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.23 (m, 10H), 5.74 (dd, *J* = 2.0, 1.4 Hz, 1H), 5.53 (ddd, *J* = 9.6, 2.0, 1.4 Hz, 1H), 4.72 (dd, *J* = 2.0, 1.4 Hz, 1H), 4.20 (d, *J* = 9.6, 1H); 74% ee, retention time 6.5 min (major) and 7.1 min (minor) on Chiralpak AY3 (5% IPA/hexane, 1.0 mL/min).



(+)-**29d**

3-Methylene-4-tridecyloxetan-2-one ([+]-29d). The general procedure was followed using racemic **29d** (53 mg, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc 98:2) provided (+)-**29d** as a colorless oil (21 mg, 40%):[17] $[\alpha]^{20}_{D}$ = (+)-37.0 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 1.9, 1.9 Hz, 1H), 5.39 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.92 (dddd, *J* = 6.5, 6.5, 1.6, 1.6 Hz, 1H), 1.81 (dddd, *J* = 7.1, 7.1, 7.1, 0.0 Hz, 1H), 1.81 (dddd, *J* = 7.8, 7.8, 7.8, 0.0 Hz, 1H), 1.46–1.40 (m, 2H), 1.33–1.22 (m, 20H), 0.84 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 146.6, 114.8, 79.7, 33.4, 32.0, 29.8, 29.7, 29.7, 29.6, 29.5, 29.5, 29.3; 56% ee, retention time 10.1 min (major) and 10.8 min (minor) on Chiralpak AY3 (5% IPA/hexane, 0.5 mL/min).



(+)-**29e**

4-Hexyl-3-methyleneoxetan-2-one ([+]29e). The general procedure was followed using racemic **29e** (34 mg, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc 94:4) provided (+)-**29e** as a colorless oil (13 mg, 38%): $[\alpha]^{20}_{D}$ = (+)-40.1 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.39 (dd, *J* = 1.6, 1.6 Hz, 1H), 4.92 (dddd, *J* = 6.6, 6.6, 1.8, 1.8 Hz, 1H), 1.80 (ddd, *J* = 7.4, 7.4, 7.4 Hz, 2H), 1.46–1.37 (m, 2H), 1.33–1.24 (m, 6H), 0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 146.5, 114.9, 79.7, 33.4, 31.6, 29.0, 24.6, 22.5, 14.1; 72% ee, retention time 5.5 min (minor) and 6.8 min (major) on Chiralpak AY3 (5% IPA/hexane, 0.5 mL/min).

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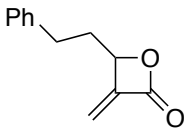
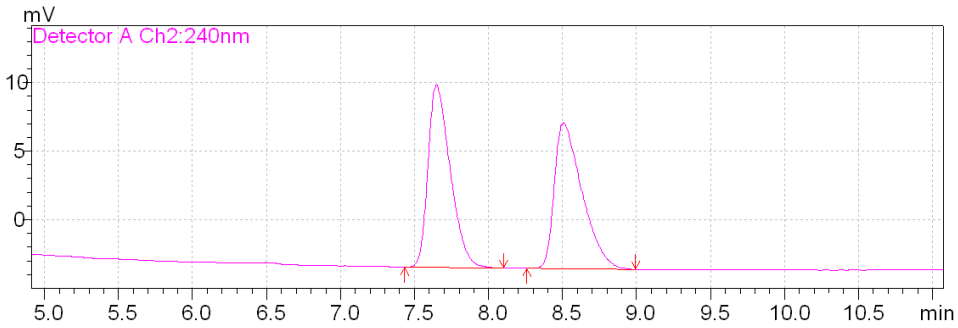
APPENDICES

A. HPLC traces



rac-**29a**

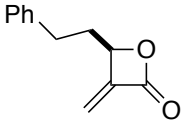


PeakTable

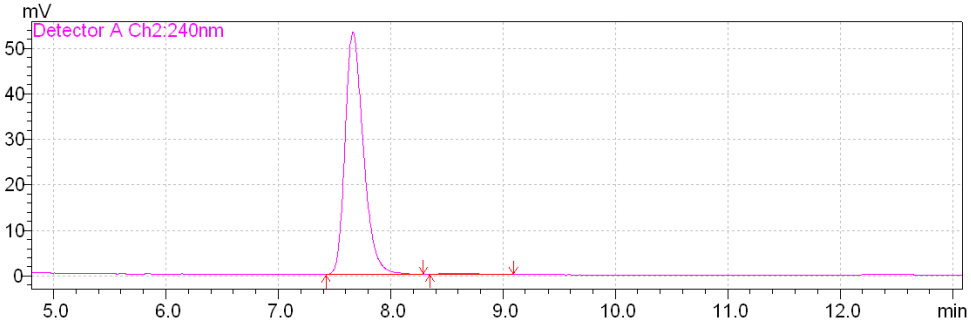
Detector A Ch2 240nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.647	139909	13317	50.122	55.617
2	8.506	139226	10628	49.878	44.383
Total		279135	23945	100.000	100.000

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 1.0 mL/min



(+)-(*R*)-**29a**
99% ee, $[\alpha]_D$ +60.3

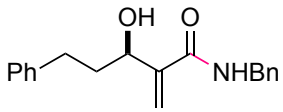


PeakTable

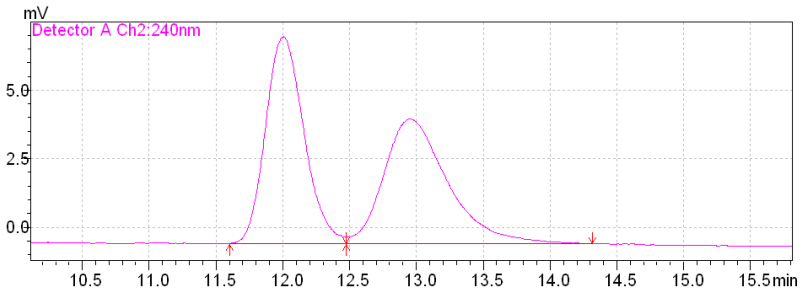
Detector A Ch2 240nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.663	602159	53267	99.325	99.660
2	8.566	4090	182	0.675	0.340
Total		606249	53449	100.000	100.000

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 1.0 mL/min



rac-**40a**

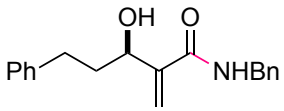


PeakTable

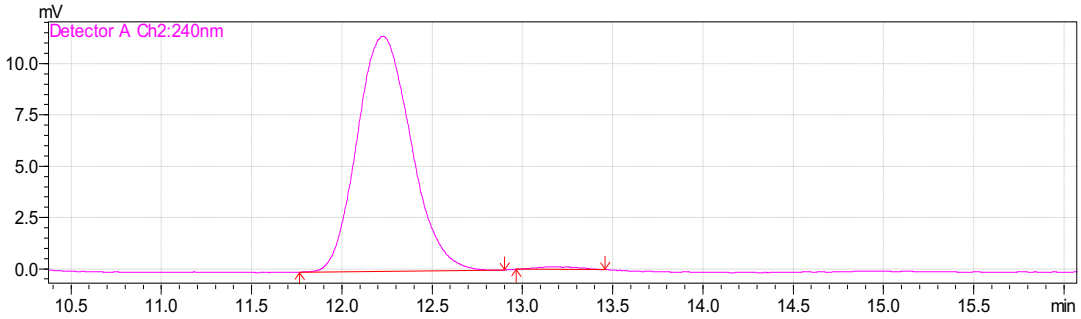
Detector A Ch2 240nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.003	151325	7555	49.951	62.394
2	12.949	151623	4553	50.049	37.606
Total		302948	12108	100.000	100.000

Method: Chiralcel OJ (Particle size: 3 um; column size: 4.6 x 250 mm)
2.0% IPA/hexane; 1.5 mL/min



(+)-(*R*)-**40a**
99% ee; $[\alpha]_D$ +24.8

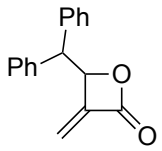


PeakTable

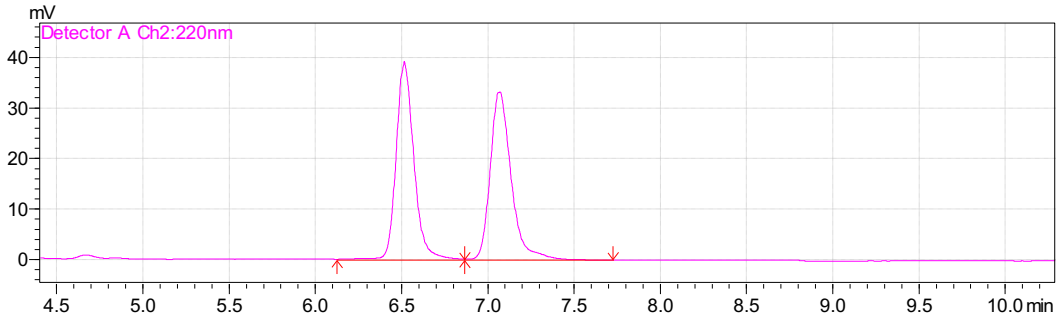
Detector A Ch2 240nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.224	237876	11461	99.626	99.361
2	13.182	893	74	0.374	0.639
Total		238769	11534	100.000	100.000

Method: Chiralcel OJ (Particle size: 3 um; column size: 4.6 x 250 mm)
2.0% IPA/hexane; 1.5 mL/min

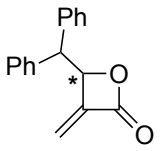


rac-**29b**

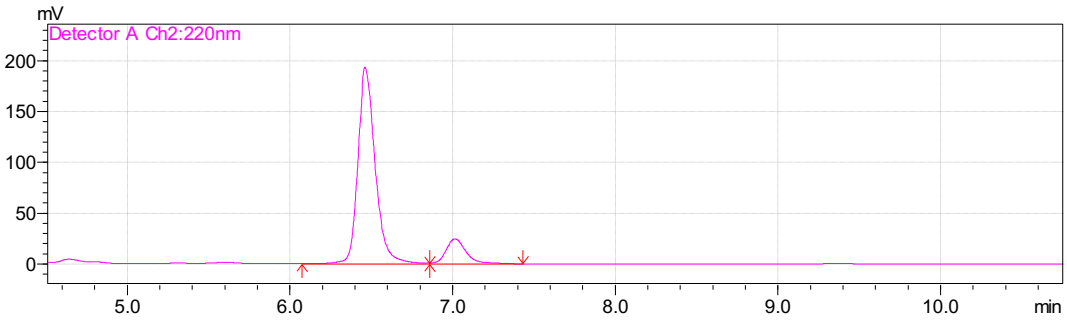


Retention time		Area	Height	% Area
RT6.514	6.514	283650	38926	50.1704
RT7.067	7.067	281724	33203	49.8296

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 1.0 mL/min

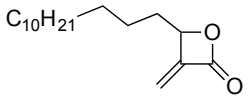


(+)-**29b** (37% yield)
74% ee, $[\alpha]_D$ +51.4

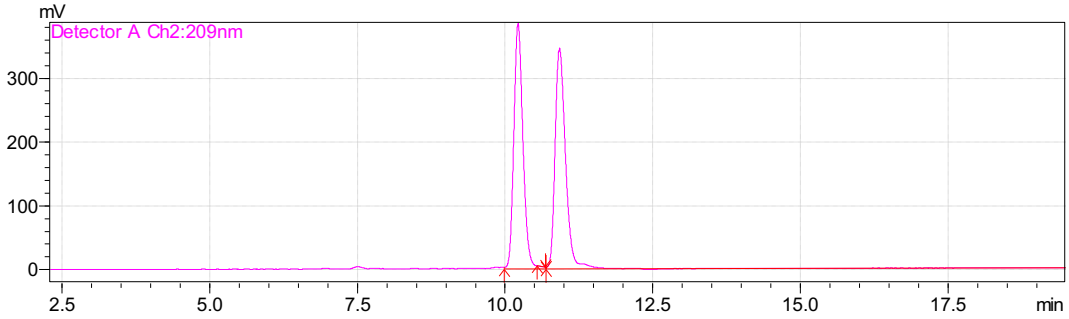


Retention time	Area	Height	% Area
RT6.462	1431262	193060	87.0550
RT7.013	212827	24595	12.9450

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 1.0 mL/min

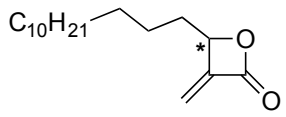


rac-**29d**

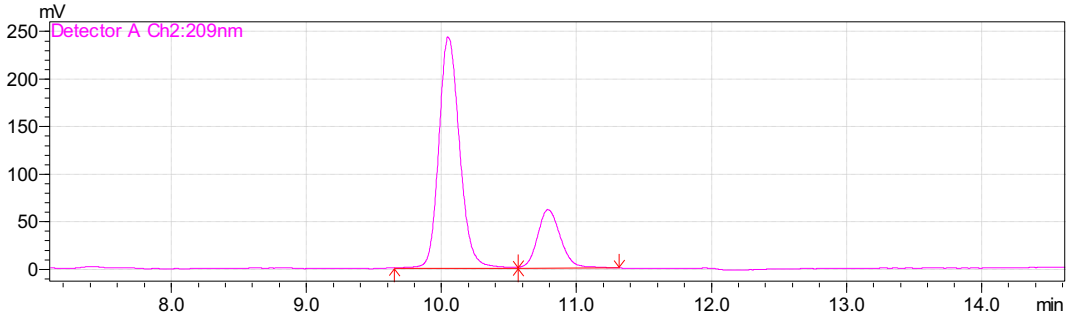


Retention time		Area	Height	% Area
RT10.120	10.120	4153842	383727	50.3263
RT10.882	10.882	4100737	345173	49.6829

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 0.5 mL/min

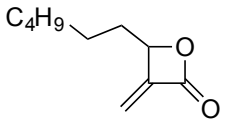


(+)-**29d** (40% yield)
56% ee, $[\alpha]_D$ +37.0

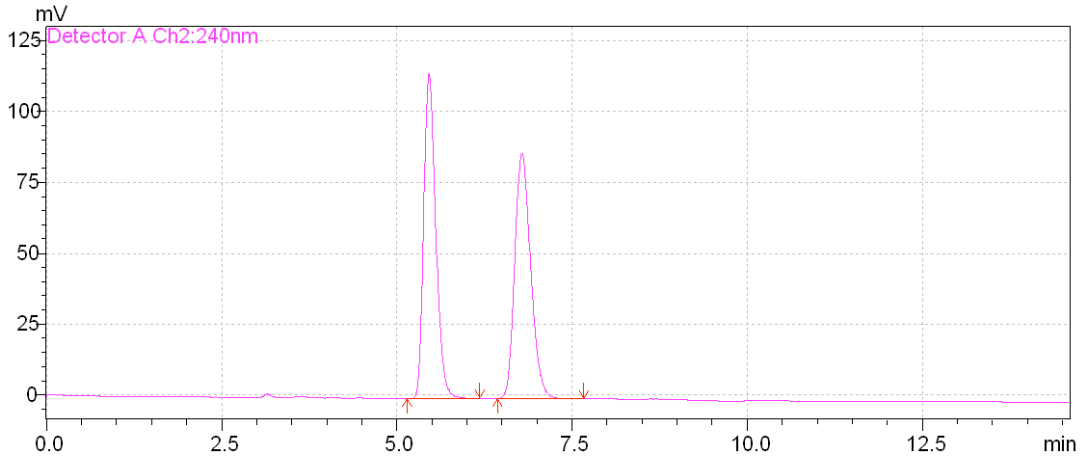


Retention time		Area	Height	% Area
RT10.068	10.068	2613948	243431	78.3454
RT10.788	10.788	722495	61480	21.6546

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 0.5 mL/min



rac-**29e**

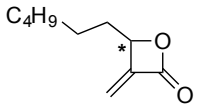


PeakTable

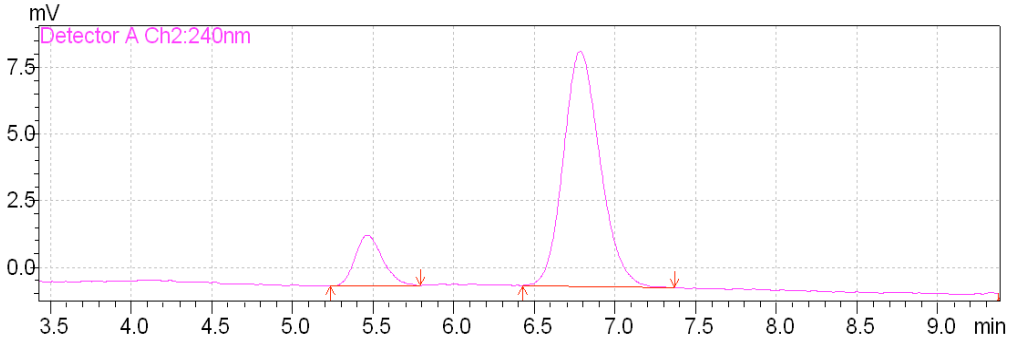
Detector A Ch2 240nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.456	1370855	114447	50.033	56.991
2	6.784	1369060	86369	49.967	43.009
Total		2739916	200816	100.000	100.000

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 1.0 mL/min



(+)-**29e** (38% yield)
72% ee, $[\alpha]_D$ +40.1



PeakTable

Detector A Ch2 240nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.463	22509	1902	13.880	17.748
2	6.784	139655	8816	86.120	82.252
Total		162164	10719	100.000	100.000

Method: Chiralpak AY3 (Particle size: 3 um; column size: 4.6 x 250 mm)
5.0% IPA/hexane; 1.0 mL/min