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Review

C−H Functionalization as a Powerful Method for Direct Synthesis of Lactones

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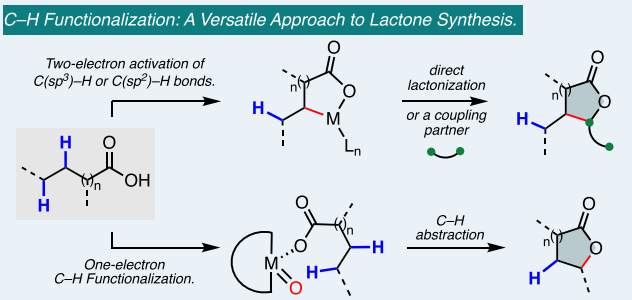
ABSTRACT: C−H activation has profoundly impacted synthetic chemistry by expanding the capabilities for the installation of functional groups and useful synthetic handles at otherwise inert C−H positions. In the context of lactone synthesis, advances in transition metal-catalyzed C−H activation have enabled the direct functionalization of unactivated C−H bonds using common, native coordinating functionalities such as carboxylic acids or amides without the need for harsh reaction conditions employed in traditional approaches or removal of strongly coordinating directing groups. This review highlights the evolution of enabling C−H lactonization strategies from initial discoveries of one- and two-electron functionalization reactivity to modern methods that leverage the combination of finely tuned ligands and reaction conditions for regioselective and enantioselective lactone synthesis. Mechanistic insights and synthetic applications are presented for lactones synthesized via C(sp^2)−H and C(sp^3)−H activation, with a focus on olefination, alkylation, hydroxylation, direct lactonization, and biocatalytic processes. The application of these methods for the preparation of complex molecules underscores the utility and impact of these methodologies in the toolkit of modern organic synthesis. By showcasing these advancements, this review aims to encourage the use of C−H activation and functionalization strategies for the efficient, regioselective preparation of lactones and the design of synthetic routes to lactones for a myriad of applications.



KEYWORDS: *C−H Activation, Asymmetric Catalysis, Lactones, Biocatalysis, Total Synthesis*

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1. INTRODUCTION

Lactones represent an important functional group in natural products, pharmaceuticals, and synthetic building blocks.[1] Thousands of naturally occurring lactones have been identified, and they hold significant structural and functional roles in pheromones,[2] antibiotics,[3] insecticides,[4] fragrances,[5] and cytotoxic agents.[6] In addition to their frequent incorporation in bioactive small molecule scaffolds, their use as a strategic functional group handle in complex molecule synthesis underscores the need for their efficient preparation.

Historically, lactones have been prepared using classical disconnection strategies between hydroxyl groups and carbonyls that often employ harsh reaction conditions such as high temperatures in the presence of strong base or acid (Figure 1A).[7] However, recent advances in transition metal-catalyzed C−H activation have revolutionized the synthetic pathways available for lactone formation.[8] Early C−H activation strategies relied on the use of strong directing groups such as aminoquinolimides or pyridines to recruit the metal catalyst to the desired location of reactivity and to differentiate between several unactivated C−H bonds.[9] However, due to extensive research progress, modern C−H activation reactions now allow the direct functionalization of simple substrates utilizing native coordinating functionalities such as carboxylic acids,[10] alkyl amines,[11] or alcohols[12] to guide the metal catalyst to selectively activate a specific C−H position and generate intermediates that can subsequently lactonize (Figure 1B). Fine-tuning ligand structures by modifying their electronics and bite angles in combination with developing reaction conditions provides chemists with the ability to access a variety of complex lactone products from easily accessible substrates.[13] Decades of advancements have expanded and improved synthetic pathways to lactones via the transition metal-catalyzed activation of C(sp^2)−H and C(sp^3)−H bonds in metrics of efficiency, regioselectivity, and enantioselectivity.

This review will explore the developments in the synthesis of lactones via transition metal-catalyzed C−H activation and C−H functionalization from the past to the present era. The text will be organized into two- and one-electron C(sp^2)−H and

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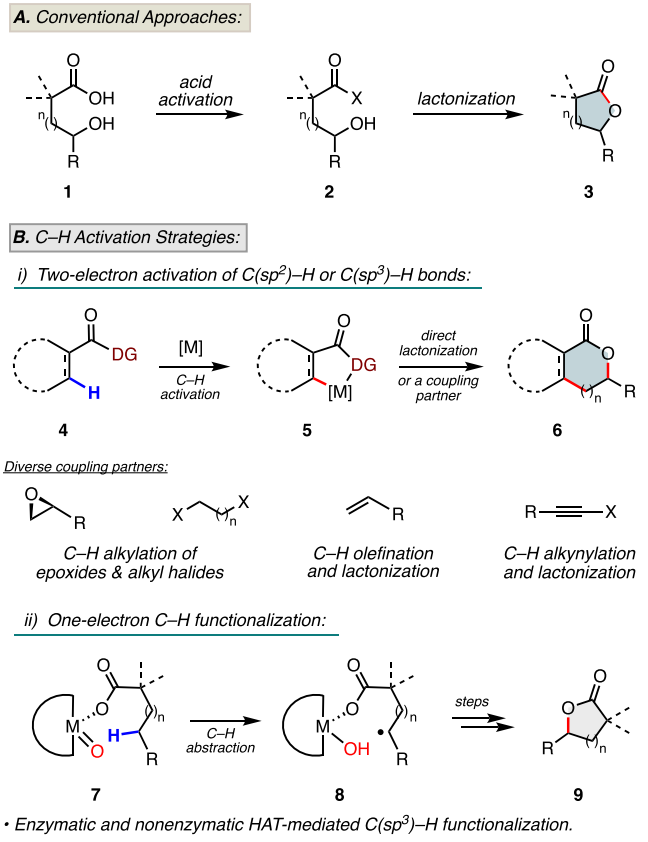
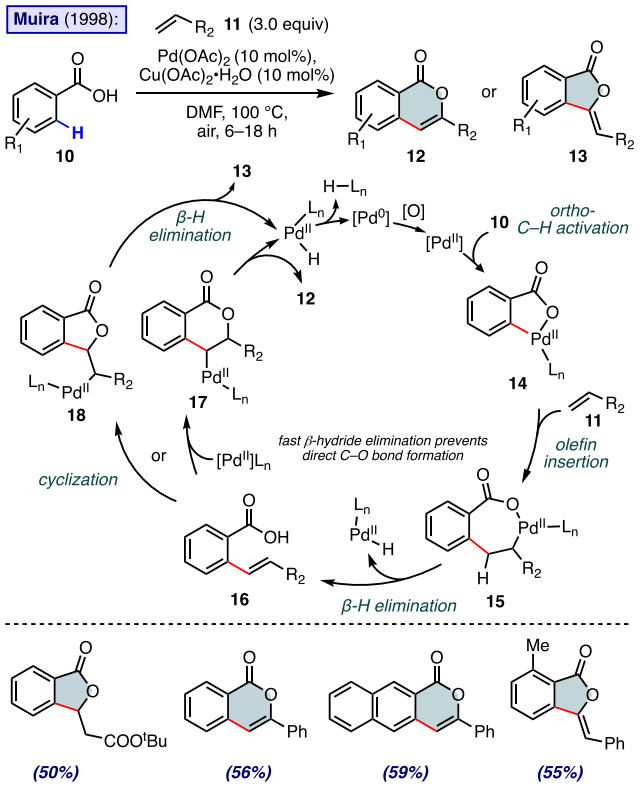


Figure 1. Overview of conventional and C−H activation strategies for the preparation of lactones.

Scheme 1. Synthesis of Benzylidenephthalides or Isocoumarins via *ortho*-C(sp^2)−H Olefination



$C(sp^3)$−H activation reactions, with subsections for olefination, alkylation, hydroxylation, direct lactonization and biocatalytic reactions. The scope of the transition metal-catalyzed processes, relevant mechanistic insights, and examples of application of these methods to the total synthesis of complex molecules will be highlighted, demonstrating the profound impact of these methods on advancing our understanding of C−H activation, lactone preparation and modern organic synthesis. The discussion of these examples may further inspire chemists to adopt C−H activation/functionalization strategies in designing synthetic routes to complex substrates and natural product targets.

2. LACTONE SYNTHESIS VIA TWO-ELECTRON C(SP^2)−H ACTIVATION STRATEGIES

Lactone syntheses via $C(sp^2)$−H activation strategies represent some of the earliest examples of carboxylate-directed C−H activation reactions. The reactivity of the key *ortho*-metalated intermediates enables coupling to diverse reaction partners including olefins, epoxides, alkyl halides, alkynes and carbon monoxide, resulting in many available approaches for lactone construction. In this section, we summarize various reports on $C(sp^2)$−H lactonization, including the scope of lactones they can be used to access, and discuss the mechanistic considerations underlying each type of transformation.

2.1. *ortho*-C(sp^2)−H Olefination and Lactonizations. Inspired by the exploratory work of Larock[14] that employed thallated carboxylic acids, Miura and co-workers disclosed the first known example of benzylic C−H lactonization reaction in 1998 transforming benzoic acid derivatives into isocoumarins (**12**) or benzylidenephthalides (**13**) products (Scheme 1).[15]

They demonstrated that the direct $C(sp^2)$−H *ortho*-palladation could proceed without the need for the preinstallation of an *ortho*-thallium group while copper acetate could act as the terminal oxidant to regenerate the Pd(II) species. Mechanistically, the carboxylate directs the $C(sp^2)$−H palladation to the *ortho*-position resulting in the palladacycle **14**. This is followed by an olefin insertion that generates the intermediate seven-membered palladacycle **15**. Direct lactonization of this intermediate is prevented by kinetically favorable *β*-hydride elimination (**15** → **16**). However, ensuing oxidative cyclization of **16** first generates the alkyl palladium species **17** or **18**, which upon a *β*-hydride elimination step provide the lactone products **12** and **13**, respectively. Depending on the substrates used, either the five-membered benzylidenephthalides or six-membered isocoumarins were obtained as the lactone products between 34−59% yield (Scheme 1). In the case of *para*-methoxy benzoic acid, both products were obtained in a 1.9:1 ratio with the isocoumarin product as the major product. The authors postulated that the steric or electronic nature of the substituents on the benzoic acid was one of the factors that determined whether the reaction would generate the six-membered isocoumarins or five-membered benzylidenephthalide products. Specifically, the presence of an *ortho*-substituent of the benzoic environment can hinder direct addition of the carboxylic acid's oxygen to the proximal position of the pendant olefin group during the oxidative cyclization (**16** → **17** or **18**) favoring the formation of the six-membered product via **16** → **17**. This was further corroborated in a report by Lee and co-workers in 2013 that described a similar approach to isocoumarins and benzylidenephthalides utilizing a palladium-(II)/silver(I) system with substituted benzoic acids and vinyl arenes.[16]

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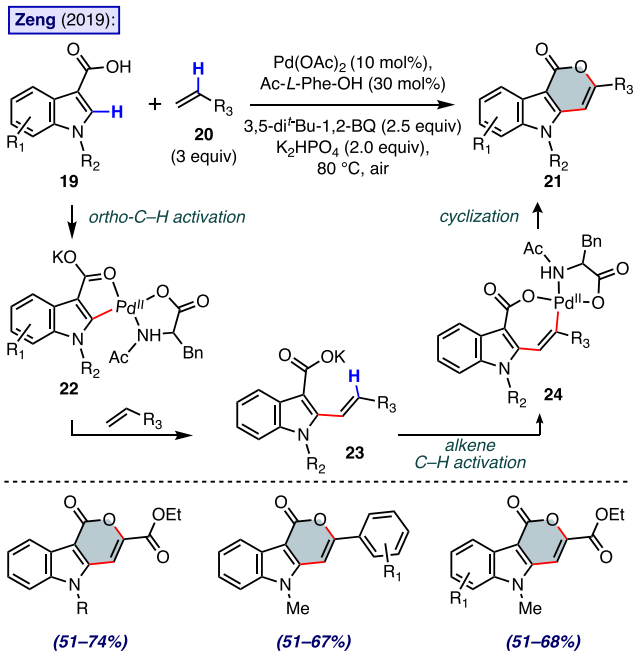
Later, the Zeng group published a method specifically focusing on the construction of pyranoindolones (**21**) in 2019 (Scheme 2).[17] Unlike prior reports, their method was selective

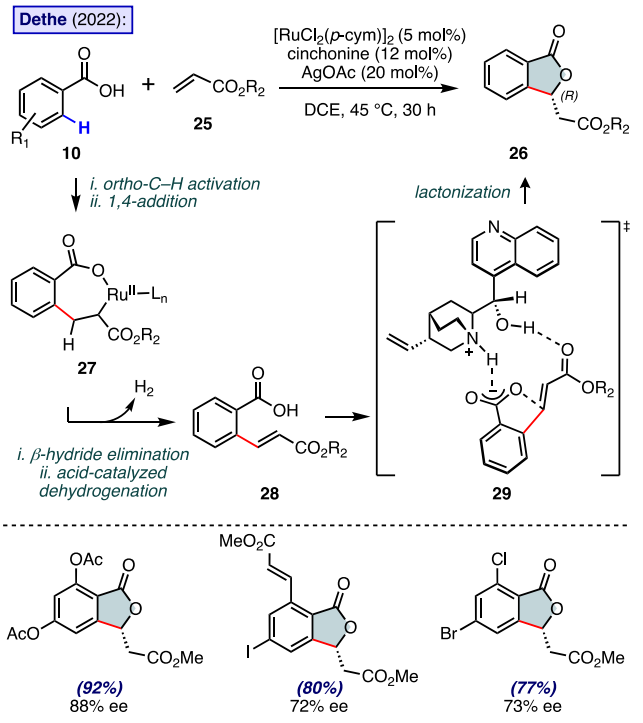
Scheme 2. Preparation of Pyranoindolones from Indole-3-Carboxylic Acids



for the six-membered lactone products across a variety of acrylates, vinyl arenes, and substituted indole-3-carboxylic acids. Using *N*-acetyl-phenylalanine as the ligand and 3,5-di-*tert*-bu-tyl-1,2-benzoquinone as the external oxidant, the pyrano[4,3-*b*]indol-1(5H)-one products were generated in moderate yields with variations on the indole nitrogen as well as the aryl and acrylate coupling partners. Based on deuterium labeling experiments, the authors proposed a 2-fold C(sp^2)−H activation mechanism is operative in their reaction manifold. Following the initial *ortho*-palladation and olefination to arrive at intermediate **23**, a second carboxylate-directed C−H activation event occurs at the remote alkene position (**23** → **24**) to form a seven-membered palladacycle, which generates the six-membered lactone products **21** following reductive elimination.

In 2022, Dethe and co-workers reported an enantioselective C−H lactonization reaction for the preparation of enantiopure benzylidenephthalides from carboxylic acids and acrylates using a ruthenium−cinchonine dual catalytic system (Scheme 3).[18] Analogous to carboxylate-directed palladium-catalyzed lactonizations, a seven-membered ruthenium metallocycle **27** is generated following *ortho*-C−H activation and 1,4-addition into the acrylate **25**. *β*-hydride elimination and acid-catalyzed dehydrogenation of the resultant ruthenium-hydride species (not shown) generates the olefinated intermediate **28**. The authors postulate that this intermediate coordinates to cinchonine via a transition state **29**, where the quinuclidine nitrogen forms an ion pair with the carboxylate and the hydroxyl group activates the alkene for intramolecular oxa-Michael addition to the *Re*-face to generate the (*R*)-enantiomer products. The authors reported a variety of functionalized benzylidenephthalide products in 68−95% yield and 35−94% ee.

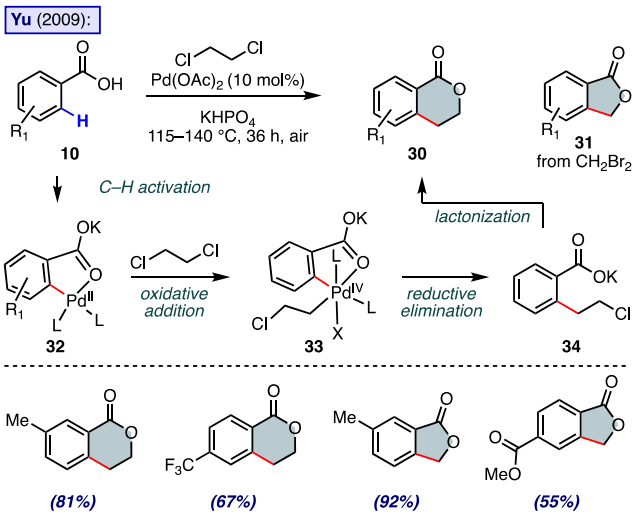
Scheme 3. Asymmetric Ru/Cinchonine-Catalyzed Coupling between Benzoic Acids and Acrylates



2.2. *ortho*-C(sp^2)−H Alkylation and Lactonizations.

Similar isocoumarin or benzylidenephthalide scaffolds have also been prepared via C(sp^2)−H *ortho*-alkylation (Scheme 4).

Scheme 4. Lactones via a Pd(II)-Catalyzed Alkylation of Benzoic Acids with Alkyl Chlorides



Yu and co-workers pioneered this approach in 2009 when they reported that simple halocarbons could provide five- or six-membered benzolactones when employing dibromomethane or dichloro-ethane as the reaction solvent, respectively.[19] In this reaction manifold, the authors propose that the oxidative addition of the halocarbon to the arylpalladium(II) intermediate **32** generates a highly reactive palladium(IV) complex **33** that eliminates to provide the alkyl halide product **34** that subsequently undergoes lactonization under the basic reaction

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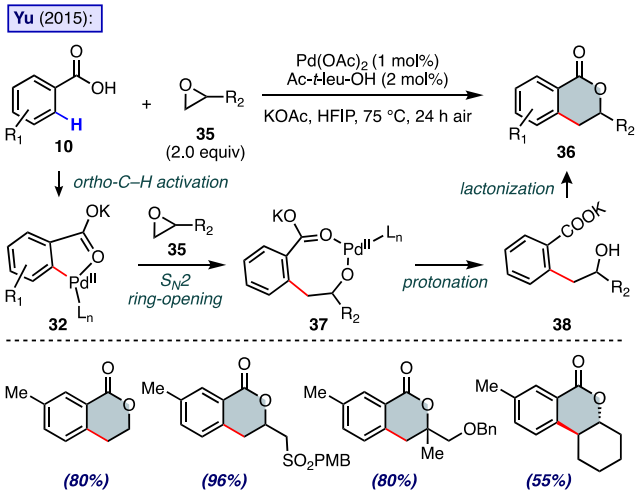
conditions. However, other pathways could also be operative in this reaction such as nucleophilic substitution of the cyclopalladate **32** on the alkyl halide as depicted in Scheme 5.

Scheme 5. *ortho*-Alkylation and Lactonization between Epoxides and Benzoic Acids

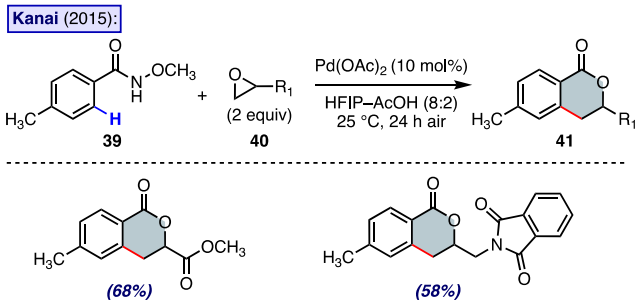


A survey of the scope revealed that a variety of electron-donating and electron-withdrawing groups were well tolerated, generating both the six- or five-membered lactones (**30** or **31**) in yields ranging from 42−92%.

Later in 2015, the Yu group reported that C(sp^2)−H *ortho*-alkylation and lactonization could also be accomplished by employing simple epoxides (Scheme 5).[20] In this approach, terminal and internal epoxides react with the *ortho*-C−H activation intermediate **32** via an S_N2 ring-opening pathway (**32** → **37**) rather than a Pd(II)/Pd(IV) mechanistic pathway. The authors propose that the resulting bicyclic palladacycle **37** can be protonated and lactonize under the basic reaction conditions. Notably, this reaction could proceed with as low as 0.5 mol % loading of palladium acetate using the mono-*N*-protected amino acid acetyl-*tert*-leucine as the ligand and provided excellent yields up to 96% when using terminal epoxides and up to 80% using internal epoxides. Stereodefined 1,2-disubstituted oxiranes could also be employed to provide the *trans*-configured products, providing stereochemical support of the proposed S_N2 reaction pathway.

The same year, Kanai and co-workers reported several lactonization examples in their work toward C(sp^2)−H *ortho*-alkylation with epoxides (Scheme 6).[21] Notably, their reaction

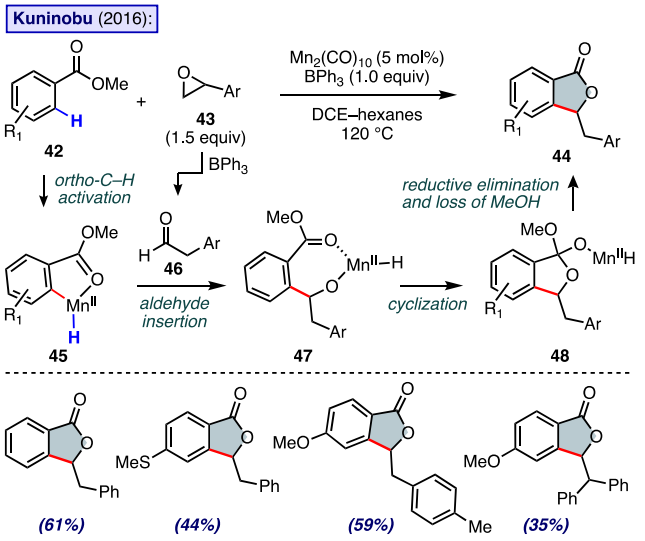
Scheme 6. Amide-Directed Coupling between Arenes and Epoxides to Synthesize Lactones



proceeds without the use of a ligand at ambient temperature when using a mixture of HFIP and acetic acid as the reaction solvents. Four terminal epoxides were surveyed and provided the lactonization products in 58−75% yield.

Kuninobu and co-workers reported a unique manganese and borane-mediated C−H alkylation of aromatic methyl esters with oxiranes in 2016 (Scheme 7).[22] This reaction is notable

Scheme 7. Manganese-Catalyzed *ortho*-Alkylation of Methyl Benzoates with Epoxides



for being the first example of a manganese-catalyzed C−H functionalization using a carboxyl-type directing group. In their proposed mechanism, the authors suggest that the triphenylborane promotes the initial *ortho*-C−H activation step as well as the isomerization of the oxirane **43** to an aldehyde **46**. Next, the aldehyde undergoes insertion into the manganese−carbon bond of **45**, followed by an intramolecular nucleophilic cyclization reaction. Ensuing reductive elimination and methanol elimination, the benzolactone product **44** is formed and the manganese catalyst regenerated. Various aromatic, heteroaromatic, and olefinic methyl esters were demonstrated to provide benzolactones in 35−90% yields with aryl and benzylic oxiranes. Notable products such as thioethers offer a valuable example of functionalization of substrates that are frequently not tolerated in palladium chemistry.

In 2018, Miura and co-workers disclosed a lactonization reaction using a nickel(II) catalyzed C−H coupling of 8-amino quinoline benzamides and epoxides under microwave conditions (Scheme 8).[23] The authors propose a plausible reaction mechanism highlighted in Scheme 8, where nickel(II) is initially reduced to nickel(I). This then undergoes a directed *ortho*-C−H cleavage event to generate the nickel(I) complex **52** and liberate HX. Subsequent oxidative addition of the epoxide generates a nickel(III) intermediate **53** which undergoes reductive elimination to forge the new C−C bond in **54**. Protonolysis then liberates the nickel(I) species which re-enters the catalytic cycle while the resulting amide **55** undergoes an intramolecular alcoholysis to generate the isocoumarin products **51** and release an equivalent of 8-aminoquinoline. This reaction pathway is supported by the absolute retention of the stereochemistry in the product from the epoxide coupling partner, rather than inversion via an S_N2 mechanism. A variety of aromatic benzamides were alkylated in

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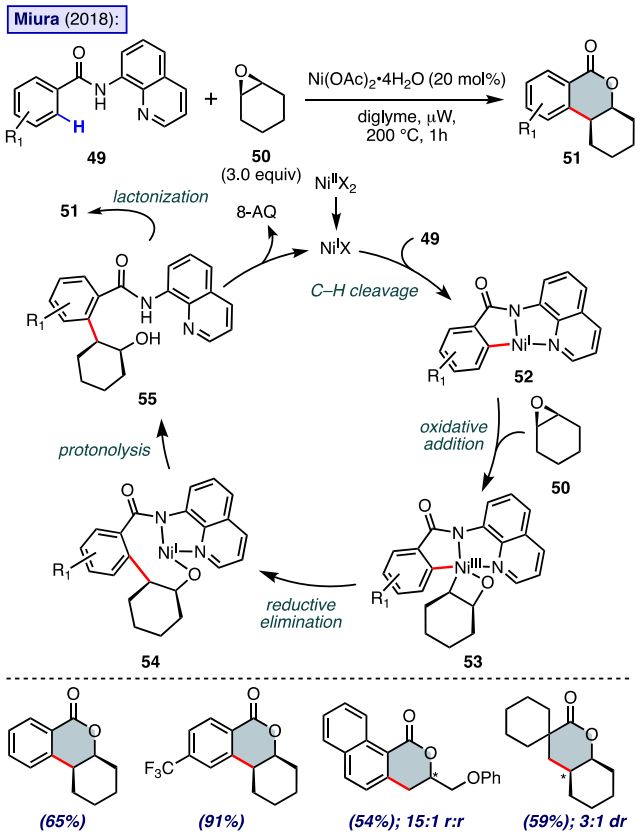
Scheme 8. Nickel(II)-Catalyzed Lactonization

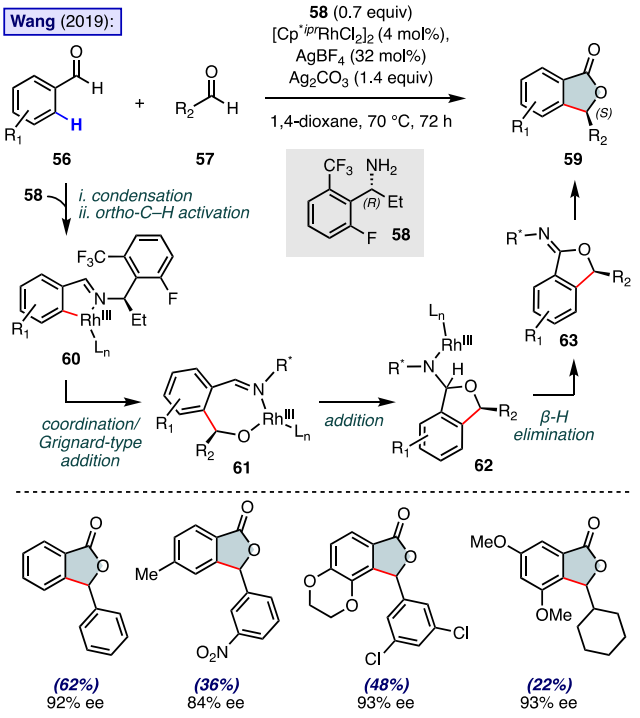


yields up to 96% with the secondary epoxide oxabicyclo[4.1.0]-heptane. Internal epoxides were also tolerated, with varying regioselectivities. Additionally, the authors demonstrated the scope could be extended to directed C(sp^3)−H alkylations to form mixtures of diastereomers at the fused position.

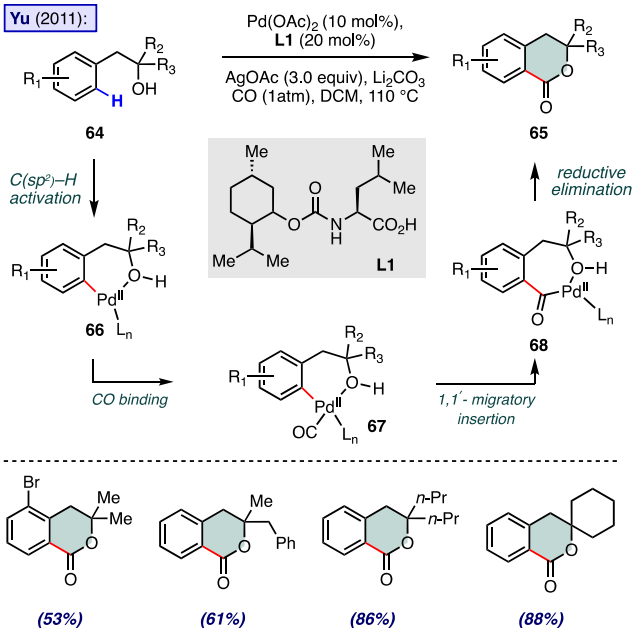
The Wang group reported an enantioselective preparation of benzylidenephthalides via a rhodium(III)-catalyzed C−H alkylation using two aldehyde coupling partners in 2019 (Scheme 9).[24] This transformation utilizes the chiral amine **58** that acts as transient directing group upon condensation with the aldehyde **56** to form an imine **60** that promotes the initial *ortho*-C−H activation to generate the chiral rhodacycle **61**. The authors suggest that this chiral metallocycle induces a high degree of diastereoselectivity during the coordination of the second aldehyde partner and this complex undergoes a Grignard-type addition of the aryl into the aldehyde carbonyl from the *Re* face to set the stereocenter. Intramolecular addition of the alkoxide into the imine generates the hemiaminal species **62** which then undergoes *β*-hydride elimination (**62** → **63**) and hydrolysis to generate the enantiopure lactone products **59**. A scope of homocoupling and heterocoupling reactions were surveyed and generally provided phthalide products in modest yields and >90%ee. Aliphatic aldehyde substrates were also tolerated in lower yields but retained the high levels of enantioselectivity.

2.3. Lactones via the Hydroxy-Directed C(sp^2)−H Carbonylation Reaction. The lactone motif can also be generated via a hydroxyl-directed C(sp^2)−H activation and carbonylation reaction (Scheme 10).[25] This protocol developed by the Yu lab utilizes phenethyl alcohol substrates (**64**) and, in one step, transforms these alcohols into isochromanones (**65**), an important structural unit in a variety of

Scheme 9. Transient Directing Group Strategy Enables Efficient Synthesis of Phthalides from Aldehydes



Scheme 10. Hydroxyl-Directed *ortho*-Carbonylation



bioactive scaffolds. The proposed reaction mechanism is initiated by a directed C(sp^2)−H activation guided by the weakly directing alcohol functionality. Binding of a carbon monoxide molecule generates the complex **66** that undergoes a 1,1′-migratory insertion into the palladium−carbon bond (**67** → **68**) generating the seven-membered palladacycle **68**. Reductive elimination delivers the lactone product **65** and Pd(0) that is readily reoxidized by the silver acetate to the catalytically active Pd(II) species. It is worth noting that the unusual (+)-menthyl containing mono-*N*-protected amino acid ligand **L1** gave the optimal yields and minimized the formation

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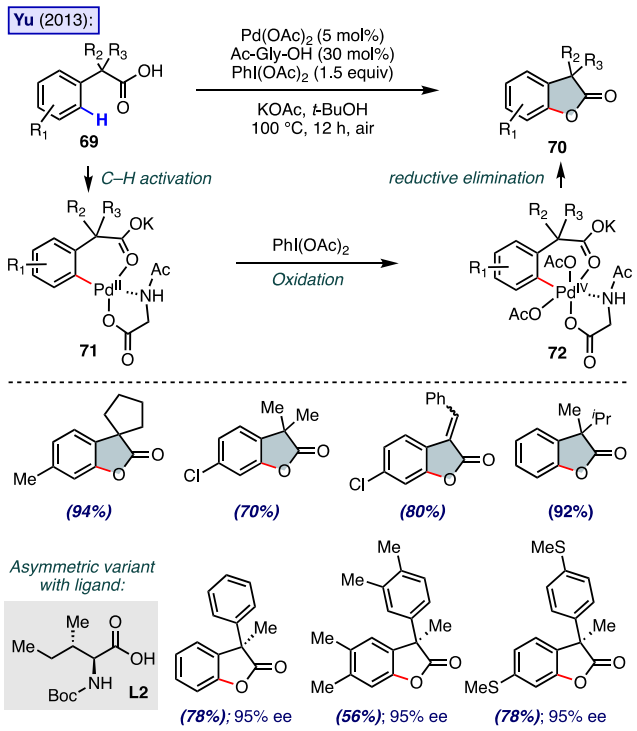
of unwanted palladium black in the presence of CO. The authors found the scope to be general with respect to the aromatic component and a variety of electron rich or poor substituents were employed in moderate to high yield.

2.4. Direct *ortho*-C(sp^2)−H Lactonization. Yu and co-workers demonstrated that phenylacetic acids can be directly lactonized via C(sp^2)−H *ortho*-lactonization in 2013 (Scheme 11).[26] In this reaction manifold, following the *ortho*-palladation

Scheme 11. *ortho*-Lactonization of Phenylacetic Acids

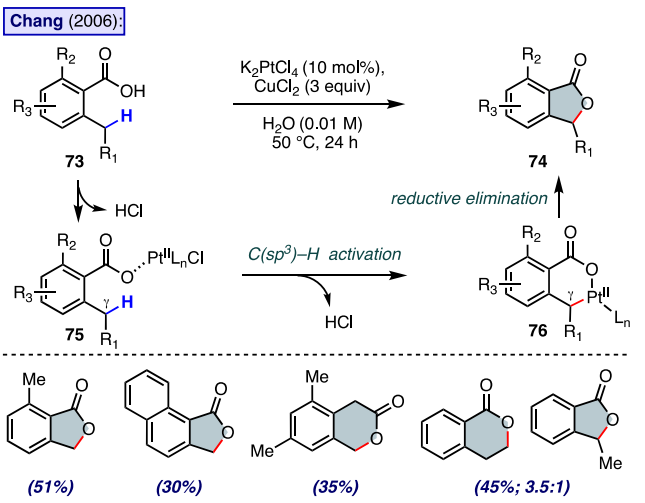


step, the palladium(II) species **71** is oxidized to the palladium(IV) complex **72** by an external oxidant such as phenyliodonium diacetate. The lactone product **70** is then generated directly upon reductive elimination from the high energy complex. The scope was investigated with respect to the aryl substituents and α,α-disubstituted phenylacetic acids. The corresponding benzofuranones lactone products could be obtained in up to 94% yield on aromatic substrates with electron donating substituents. Electron-withdrawing groups and thiofuran in place of the phenyl ring were also tolerated. Impressively, the authors demonstrated that this reaction could be rendered enantioselective with diphenylacetic acids by employing *N*-Boc isoleucine amino acid (**L2**) as the ligand with only slightly modified reaction conditions providing a variety of enantiopure lactones in 56−86% yield and 89−96% ee.

3. TWO-ELECTRON BENZYLIC AND ALLYLIC C(SP3)−H ACTIVATION APPROACHES IN THE SYNTHESIS OF LACTONES

Early reports of lactone synthesis via two-electron C(sp^3)−H activation centered on electronically activated benzylic or allylic positions. Similar to substrates accessed via C(sp^2)−H lactonization, Lee and Chang reported a platinum-catalyzed preparation of benzylidenephthalide products **74** in 2006 (Scheme 12).[27] Mechanistically, the platinum is directed to the

Scheme 12. Synthesis of Lactones via a Benzylic C(sp^3)−H Activation with a Platinum Catalyst



benzylic position of an *ortho*-substituted benzoic acid (**75** → **76**) and a C(sp^3)−H activation event forms the six-membered platinum complex **76**. Reductive elimination then provides the benzylidenephthalide product **74** and a Pt(0) species that is readily oxidized with copper(II) chloride to regenerate the active form of the catalyst. Six benzoic acids with *ortho*-aliphatic substituents were screened and provided the five-membered lactones in moderate yields (30−56%). Employing an ethyl-substituted benzoic acid provided products derived from the activation of both primary and secondary C−H bonds in a 3.5:1 ratio favoring the less hindered methyl position of the acid substrate. In this instance, the formation of the five-membered lactone is noteworthy as it represents an early example of the C−H functionalization of a benzylic methylene.

The same year, White and co-workers reported an innovative strategy to prepare macrocyclic lactones via allylic C(sp^3)−H activation using a palladium(II) bis-sulfoxide catalyst (Scheme 13).[28] Mechanistically, the authors propose that a π-allyl palladium carboxylate species **79** acts as a templating intermediate for the C−H oxidation event that forms the lactone C−O bond. The reaction was demonstrated to be effective for the construction of various complex 14- to 19-membered macrocycles including aliphatic lactones, depsipeptides, and bisindoylmaleimide products in yields up to 62% on gram scale. This method was later applied to the synthesis of the erythromycin precursor 6-deoxyerythronolide B (**80**) in a later report in 2011 (see Scheme 42 in Section 8).[29]

Also in 2011, the White group applied a similar catalytic system to prepare *anti*-1,4-dioxan-2-ones via allylic C−H oxidation using Cr(salen)Cl and benzoquinone as additives to promote the carboxylic acid functionalization and C−O bond forming steps, respectively (Scheme 14).[30] A broad variety of aliphatic 1,4-dioxan-2-ones were prepared in modest to high diastereoselectivities and up to 83% yield.

In 2011, the Martin group disclosed that benzylidenephthalides could be readily accessed from substituted methyl benzoic acids using a palladium(II)-catalyzed and silver-mediated C(sp^3)−H activation with *N*−acetyl-*L*-leucine (**L3**) as the ligand (Scheme 15).[31] The authors propose that in addition to reoxidizing palladium, the silver may play a role in the initial transmetalation step which provides a palladium(II)

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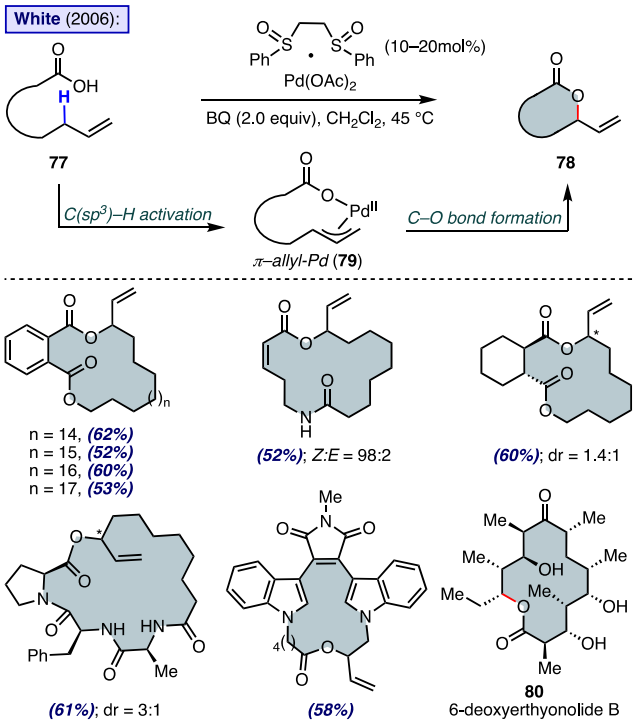
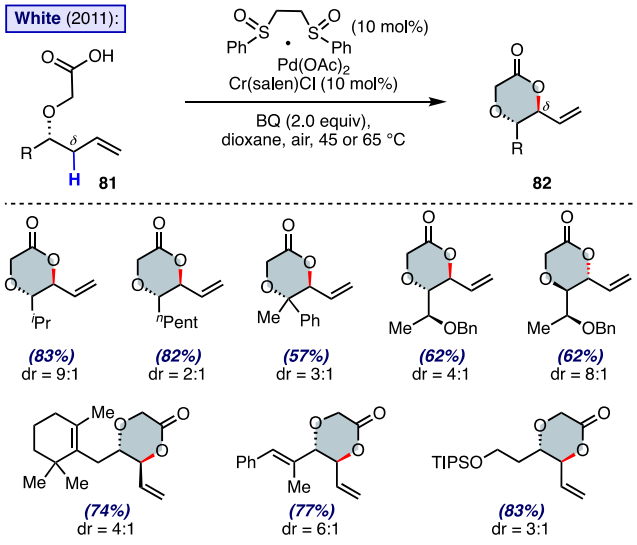
Scheme 13. Palladium-Catalyzed Synthesis of Macrocyclic Lactones via Allylic C(sp^3)−H Activation

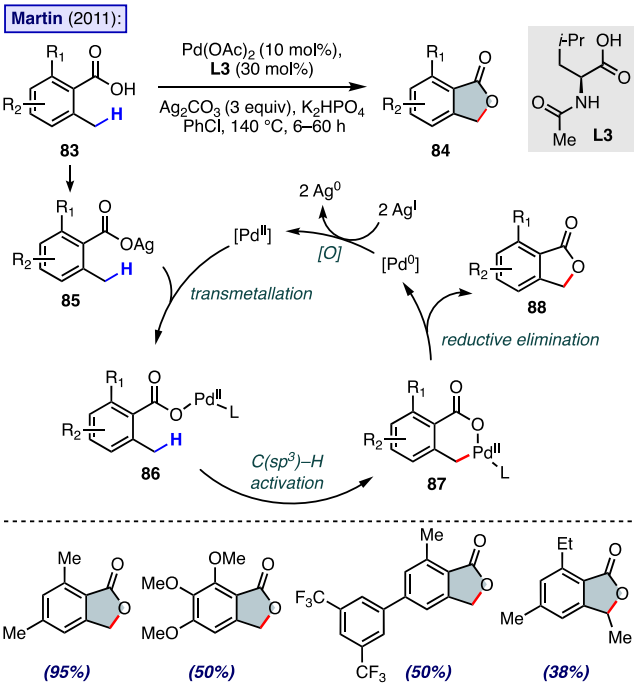


Scheme 14. Intramolecular Allylic C−H Esterification



carboxylate complex **86** prior to the *ortho*-C(sp^3)−H activation. The resulting six-membered palladacycle **87** undergoes C−O bond-forming reductive elimination to provide the benzolactone products **84**. Mechanistic experiments with isotopically labeled substrates showed no significant kinetic isotope effect suggesting that the C(sp^3)−O bond-forming reductive elimination is the rate-determining step as opposed to the C(sp^3)−H activation. This reaction was effective in functionalizing benzoic acids possessing substitutions to the 5 and 6-position that provide a steric deterrence against C(sp^2)−H activation. Aliphatic and heteroatom substituents were also well tolerated and provided the substituted lactones in yields up to 95%. Additionally, the preparation of a γ-methyl product in 38% yield suggests that this reaction manifold could be

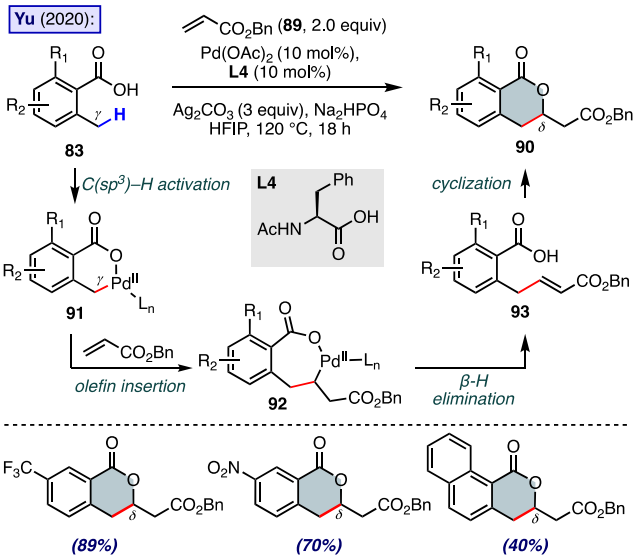
Scheme 15. Benzolactones via a Benzylic C(sp^3)−H Activation



extended to C(sp^3)−H activation of aliphatic substituents beyond methyl groups.

The Yu group also reported a lactonization to prepare δ-lactones in 2020 via γ-C(sp^3)−H olefination using methyl benzoic acids, benzyl acrylate, and acetyl-*L*-phenylalanine as the ligand (Scheme 16).[32] Mechanistically, following the acid-

Scheme 16. Benzylic Olefination and Subsequent Lactonization for the Synthesis of δ-Lactones



directed C(sp^3)−H activation, an olefin insertion forms the seven-membered palladacycle **92** that upon β-hydride elimination provides the olefinated intermediate **93**. Under the reaction conditions, the pendant carboxylic acid residue then undergoes a conjugate addition to the α,β-unsaturated ester to efficiently generate the δ-lactone products **90**. A variety

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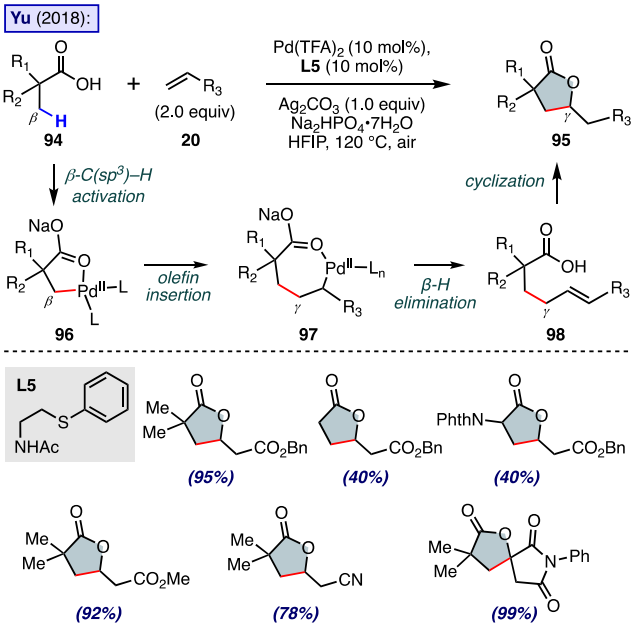
of substituted benzoic acids including those with electron-withdrawing groups and accessible δ-C(sp^2)−H bonds were well tolerated and provided the γ-C(sp^3)−H activated products in 40−89% yields. The same report also demonstrated the olefination on nonactivated aliphatic C(sp^3)−H bonds and will be described in the next section.

4. TWO-ELECTRON C(SP^3)−H ACTIVATION OF METHYL GROUPS TO ACCESS LACTONES

The functionalization of C(sp^3)−H bonds in unactivated, aliphatic substrates presents significant challenges not only in reactivity but also in differentiating multiple similar C−H bonds. Within the past decade, a variety of methods for lactone synthesis have emerged that utilize specialized ligands and conditions to drive the formation of the key palladacycles that undergo further reactivity to yield diverse lactone products.

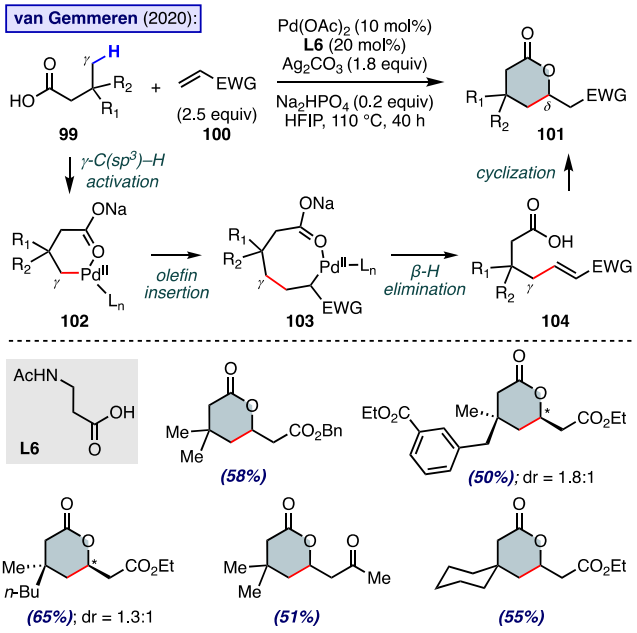
4.1. C(sp^3)−H Olefination and Lactonization Reactions. Lactonization via two-electron aliphatic C(sp^3)−H activation was first accomplished by Yu and co-workers in 2018 via β-C(sp^3)−H olefination (Scheme 17).[33] Using an unprecedented bidentate thioether ligand **L5**, Yu and co-workers were able to address a longstanding synthetic challenge and perform β-C(sp^3)−H olefination on unactivated α-methyl substituents of native carboxylic acids to synthesize γ-lactones **95**. Mechanistically, palladium(II)-catalyzed C(sp^3)−H activation forms a five-membered palladacycle **96** that undergoes an olefin insertion to form the seven-membered palladacycle **97** that provides the intermediate olefination product **98** upon β-hydride elimination. A diverse array of aliphatic substrates performed excellently under these conditions, providing γ-lactone products in up to 99% yield. As expected, α-trisubstituted substrates gave the highest yields due to their favorable Thorpe−Ingold effects that influence the preorganization of the substrate for the key C−H activation. Esters, phthalimides, amides, nitriles and maleimide substrates were all well-tolerated. Substrates without quaternary substitution were also lactonized under these conditions, albeit in lower yields.

Scheme 17. β-C(sp^3)−H Olefination of Free Aliphatic Carboxylic Acids



During 2020, three reports of lactonization via γ-C(sp^3)−H olefination of aliphatic carboxylic acids were published using β-disubstituted carboxylic acids. In the first report of γ-C(sp^3)−H olefination, van Gemmeren and co-workers utilized electron deficient olefins, palladium(II) acetate, silver carbonate, and *N*-acetyl-β-alanine as the ligand to accomplish this challenging lactonization (Scheme 18).[34] With the β-position inaccessible, the C−H activation occurs selectively at the γ-position of the free acids forming the metallocycle **102** that provides the desired δ-lactone products **101** in an otherwise analogous mechanistic pathway as described above for β-C(sp^3)−H olefination. A variety of β-quaternary δ-lactones were synthesized in moderate yields ranging from 40−67%. Kinetic isotope labeling studies were also performed and indicated that the C−H activation is the rate limiting step.

Scheme 18. Synthesis of Lactones via a γ-C(sp^3)−H Olefination of Carboxylic Acids



Next, Yu and co-workers reported similar conditions to access aliphatic δ-lactone products in 42−89% yield using various acrylates, palladium(II) acetate, silver carbonate, and *N*-acetyl-α-phenylalanine as the ligand (Scheme 19A).[35] Shortly after, Maiti and co-workers disclosed conditions for lactonization using electron-deficient olefins, palladium(II) acetate, silver carbonate, and *N*-acetyl-α-valine (Scheme 19B). Over 40 examples of β-disubstituted δ-lactones were synthesized in up to 85% yield and the chemistry was also extended to the preparation of maleimide coupling partners to provide interesting seven-membered [5.3.0] bicyclolactone products.[36]

Yu and co-workers realized an intramolecular β-C(sp^3)−H olefination and subsequent lactonization annulation reaction to prepare bicyclo[3.2.1]lactones from free carboxylic acids in 2022 (Scheme 20).[37] This unique annulation reaction proceeds via an initial carboxylic-acid directed β-C(sp^3)−H activation, followed by an intramolecular olefin migratory insertion (**107**→**108**). Ensuing β−H elimination and lactonization of the carboxylic acid to the pendant alkene provides the

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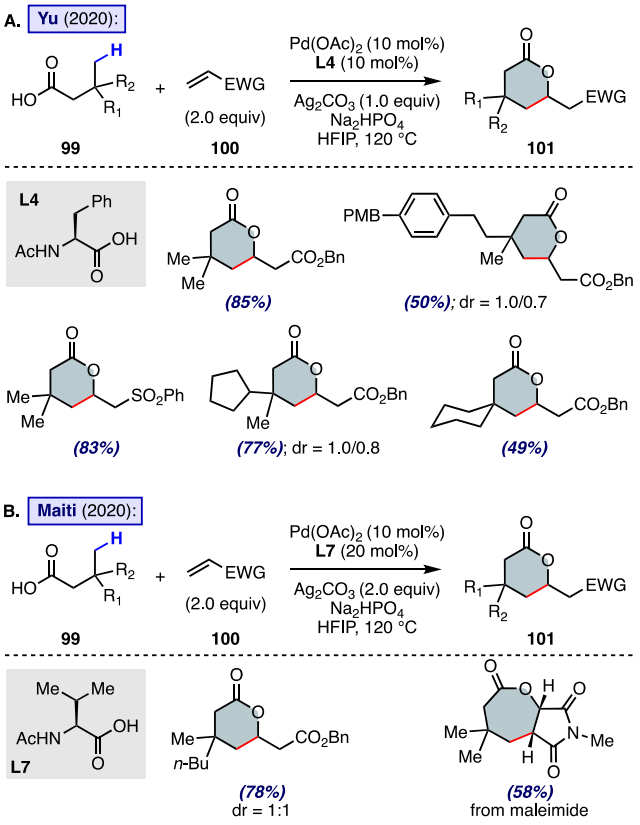
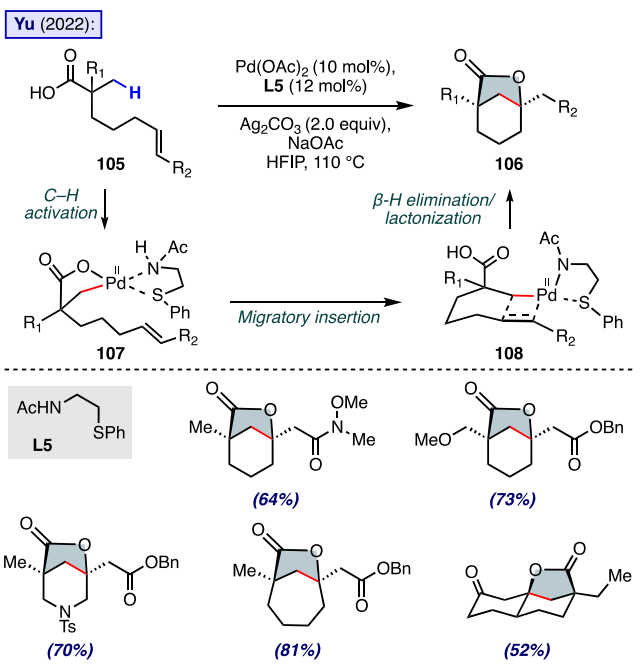
Scheme 19. Preparation of δ-Lactones via a γ-C(sp^3)−H Activation Strategy



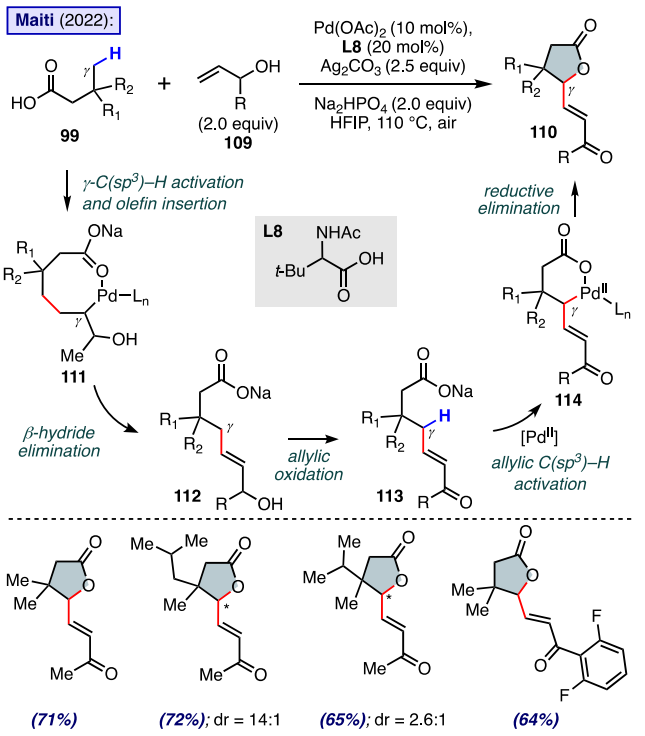
Scheme 20. Synthesis of [3.2.1] Lactones via an Intramolecular Olefination and Lactonization Sequence



bicyclo[3.2.1]lactone products **106**. The thioether ligand **L5** was uniquely enabling in this transformation and the annulation proved to be tolerant of a range of electron-withdrawing olefin functionalities, providing lactone products in yields ranging from 52−88%. Their scope also featured a seven-membered bicyclo[4.2.1]lactone (81%) and 6,6,5-tricyclic lactone (52%).

Also in 2022, Maiti and co-workers reported a dual 1,1-C(sp^3)−H activation to synthesize γ-lactones (Scheme 21).[38]

Scheme 21. Twofold-1,1-C(sp^3)−H Activation Reaction of Aliphatic Acids to Synthesize γ-Lactones



Mechanistically, two C(sp^3)−H activation events are operative to prepare these lactones possessing synthetically useful α,β-unsaturated substituents. The mechanistic sequence is thought to proceed through several carefully orchestrated steps. Starting with an initial γ-C(sp^3)−H activation, olefin insertion, and β-hydride elimination, the γ-allylic alcohol intermediate **112** is formed. Next, a palladium(0)-catalyzed allylic oxidation is followed by a second C(sp^3)−H activation event at the activated allylic position to form a six-membered palladacycle **114** that undergoes a final reductive elimination to access the γ-lactone products **110**. Mechanistic experiments using various viable reaction intermediates confirmed that formation of the allylic alcohol **112** rather than an alternative ketone intermediate was necessary to facilitate the second C−H activation event. The reaction performed best on β,β-disubstituted aliphatic acid substrates, but secondary, tertiary, primary and allylic acetates also served well as coupling partners in yields up to 73%. For applicable substrates, varying degrees of diastereoselectivity were observed from 1:1 to >20:1.

4.2. Lactone Synthesis via Direct C(sp^3)−H Lactonization. In 2019, Yu and co-workers demonstrated that β-lactone products could be directly accessed from aliphatic acids via β-C(sp^3)−H activation using a substituted *N*-acetyl protected β-amino acid as the enabling ligand via a six-membered chelate (Scheme 22).[39] The reaction pathway proceeds via a palladium (II/IV) catalytic cycle, where the intermediate palladacycle **116** following the initial C(sp^3)−H activation undergoes further oxidation with *tert*-butyl hydrogen peroxide to the

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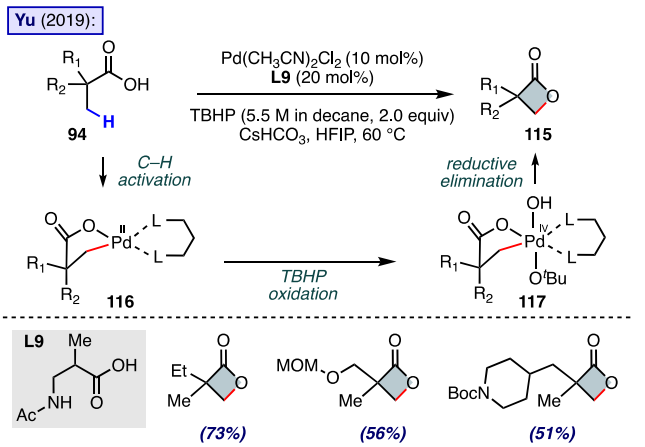
Scheme 22. β-Lactone Synthesis from Free Carboxylic Acids

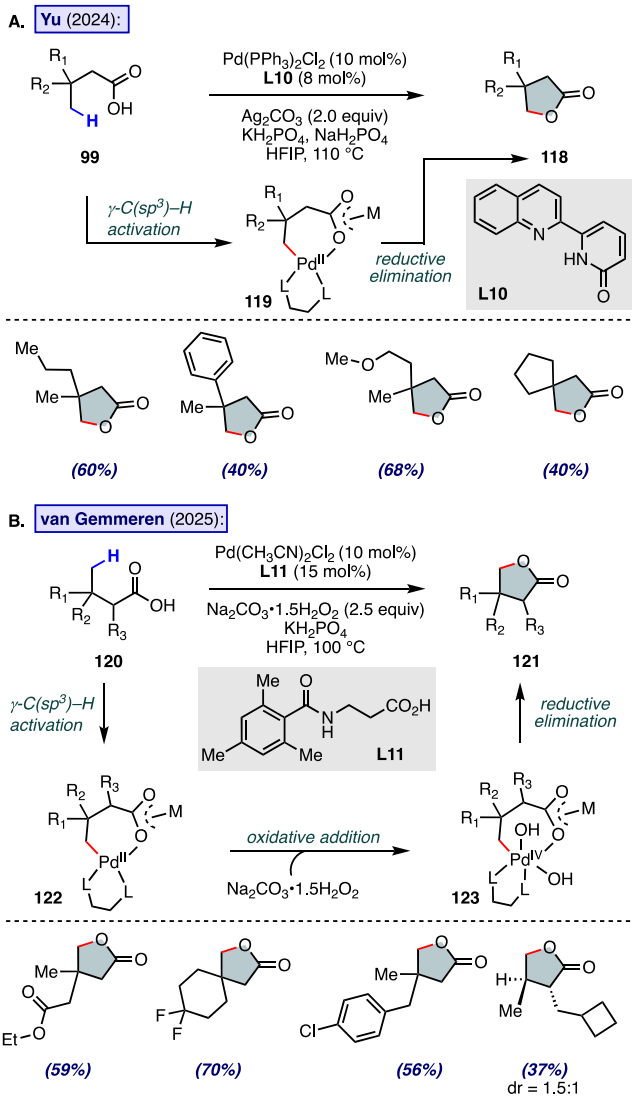


palladium(IV) complex **117**. The bite angle arising from the six-membered chelation is thought to promote the direct reductive elimination to generate the β-lactone products. A variety of α-quaternary carboxylic acids with diverse functionality were well tolerated and furnished the β-lactones in 46−94% yield. α-Disubstituted acids performed similarly well in this reaction manifold and provided the desired β-lactone products in yields as high as 82%.

In back-to-back publications Yu[40] and van Gemmeren[41] disclosed their protocols for palladium-catalyzed approaches to direct γ-lactonization reactions of aliphatic carboxylic acids (Scheme 23A and B). Both transformations are capable of effectively cyclizing a variety of acids via mechanistically distinct pathways. In the Yu lab reaction protocol, this transformation was enabled by a bidentate quinoline−pyridone ligand **L10**. Under their optimized conditions, exposure of the acid substrate to palladium catalyst in the presence of silver carbonate and a dual base system resulted in a selective γ-C(sp^3)−H activation event forming the palladacycle **119**. This alkyl palladium species then undergoes a C−O reductive elimination event forming the γ-lactone product and a palladium(0) catalyst that is subsequently oxidized to catalytically active palladium(II) species with silver carbonate. The authors found that concentrated solvent conditions (1.25M) and extended reaction times (36 h) were optimal to obtain a variety of γ-lactones in high to moderate yields. Notably, the authors also developed conditions to form γ-lactones via activation of methylene C−H bonds (see chapter 5.0).

The van Gemmeren lab's γ-lactonization reaction also enabled the preparation of a broad range of lactone products via a C−O reductive elimination, employing sodium percarbonate as the reaction oxidant (Scheme 23B). The authors identified the β-alanine−derived ligand **L11** as optimal for promoting the desired C(sp^3)−H lactonization pathway. Mechanistically, the transformation is proposed to proceed through oxidation of the palladium(II) palladacycle **122** with sodium percarbonate, generating the highly oxidized Pd(IV) complex **123**. This high-valent palladacycle then undergoes C(sp^3)−O reductive elimination to afford the γ-lactone product and regenerate the active form of the catalyst. The developed protocol proved effective across a wide range of carboxylic acids bearing diverse substitution patterns, thereby enabling the synthesis of a library of γ- lactone products. Notably, substitution at both the α- and β-positions of the acid substrates was found to be well tolerated.

Scheme 23. Pd-Catalyzed Direct γ-Lactonization of Carboxylic Acids



4.3. Lactones via an Initial C(sp^3)−H Alkynylation Reaction.

Further efforts expanded the scope of coupling partners for C−H lactonization to alkynes which provide synthetic access to butenolide lactones from carboxylic acids via a β-C(sp^3)−H alkynylation (Scheme 24).[42] Mechanistically, the butenolide formation proceeds via two β-C−H activation events. After the initial β-C(sp^3)−H activation to form a five-membered palladacycle 127, a β -hydride elimination results in the generation of an acrylate intermediate 128. This α,β-unsaturated species can then undergo a β-C(sp^2)−H activation to form a second five-membered palladacycle 129 that reacts with triisopropylsilyl (TIPS)-protected ethynyl bromide to generate a vinyl alkyne intermediate 130 that forms the γ-butenolide products 126 via oxidative cyclization. A variety of mono-α-substituted carboxylic acids were successfully coupled to TIPS-ethynyl bromide to furnish butenolide products up in up to 82% yield.

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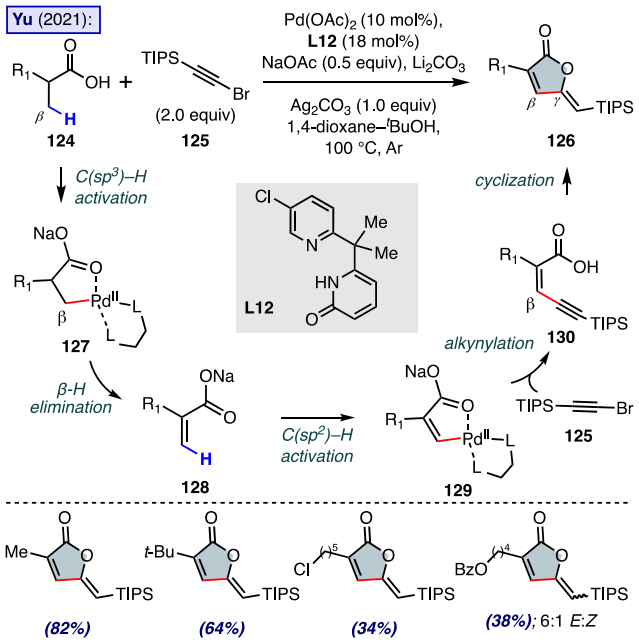
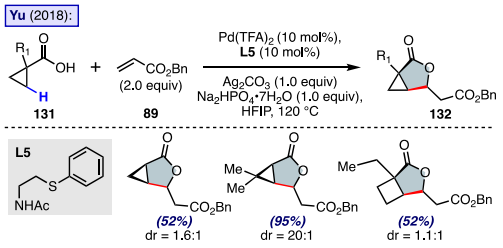
Scheme 24. Synthesis of Butenolides via a Ligand-Enabled Alkynylation and Cyclization Sequence



5. LACTONE SYNTHESIS VIA A TWO-ELECTRON ACTIVATION OF METHYLENE C(SP^3)–H BONDS

The advancements of lactonization via aliphatic C–H activation have also been applied to the activation of methylenes. Yu and co-workers' pioneering report of lactonization via β-C(sp^3)–H olefination in 2018 also featured several examples of β-C(sp^3)–H olefination of β-methylenes (Scheme 25).[33] Cyclopropanes and cyclobutanes could undergo β-C(sp^3)–H olefination with benzyl acrylate using the same thioether ligand **L5** with palladium(II) trifluoroacetate and silver carbonate. Eight examples were reported producing the bicyclo[3.1.0]- and bicyclo[3.2.0] lactone products in 42–95% yield and up to 20:1 dr in the case of the *gem*-dimethyl containing product.

Scheme 25. Lactone Synthesis via Activation of Cyclopropane and Cyclobutane Methylene C–H Bonds



Yu and co-workers showed a remarkable advance in the C(sp^3)–H activation of methylenes in 2022 using a judicious choice of palladium catalyst and ligand to effect β-C(sp^3)–H lactonization or γ-C(sp^3)–H lactonization of aliphatic dicarboxylic acid substrates (Scheme 26).[43] The six-carbon adipic acid type substrates **133** could undergo β-C(sp^3)–H activation and lactonization using palladium(II) acetate, silver carbonate, the quinoline–pyridone ligand **L10**, and para-xyloquinone as an additive known to promote reductive elimination. Preliminary mechanistic experiments suggested that the initial C(sp^3)–H activation step occurs selectively at the β-position in adipic acid substrates (Scheme 26A). While the precise mechanism of the subsequent lactone formation is not fully understood, subjecting (*E*)-hex-2-enedioic acid to the reaction conditions provided the expected lactonization product in diminished yield. This led the authors to suggest that two mechanistic pathways for the final C–O bond formation may be occurring simultaneously: one arising from intramolecular lactonization via conjugate addition and a second arising from reductive elimination at palladium. Using the optimal reaction conditions, adipic acids possessing a range of aliphatic and heteroatom substituents could be efficiently transformed into γ-lactones in moderate 50–70% yields. The reaction proved tolerant of varying substituents at the α-position, and unsubstituted, monosubstituted, and disubstituted substrates gave the lactonization products in similar yields.

Similarly, the seven-carbon pimelic-acid type substrates **137** (Scheme 26B) provided six-membered lactone products **138** via an analogous initial β-C(sp^3)–H activation step followed by lactonization using the same reaction conditions with ligand **L10**. Aliphatic acids with β-substituents and aromatic subunits could be employed to produce the six-membered ring containing lactone products in 30–85% yield. Alkyl and heteroatom substituents were well tolerated. Additionally, Yu and co-workers demonstrated that further homologated dicarboxylic acid substrates could be biased to synthesize five-membered γ-lactones by modifying the ligand to the homologated *gem*-dimethyl containing quinoline–pyridone **L13** that forms a six-membered chelate with the palladium catalyst (Scheme 26C). This ligand-enabled extension of the methodology is notable considering the presence of competing β-methylenes that can form the kinetically and thermodynamically favorable five-membered palladacycle upon β-C(sp^3)–H activation. Moreover, this γ-C(sp^3)–H activation pathway leading to the gamma-C–O bond formation was corroborated by extensive deuterium labeling experiments.

Also in 2022, the Yu reported a method for preparing β-alkylidene-γ-lactones from cyclic or acyclic carboxylic acid substrates and activated olefins using a tandem dehydrogenation–olefination–lactonization reaction that proceeds via two C–H activation events (Scheme 27).[44] The initial dehydrogenation event occurs via β-C(sp^3)–H activation of the β-methylene position followed by β-hydride elimination providing alkene **145**. A second C(sp^2)–H activation event occurs at the proximal position of the alkene and forms the five-membered palladacycle **146**. Next, olefin insertion is followed by a β-hydride elimination generating the α,β-unsaturated intermediate **147**, which undergoes an intramolecular Michael addition to construct the lactone functionality. The chemistry proved effective for constructing α-substituted bicyclic lactones in a variety of ring sizes with moderate to excellent diastereoselectivity in yields up to 82%. Additionally, 12 acyclic substrates were successfully converted to the corresponding β-alkylidene-γ-lactones in 38–74% yield and modest diastereoselectivity.

The next year, the Maiti group disclosed a direct lactonization of aliphatic cyclic carboxylic acid substrates via methylene selective γ-C(sp^3)–H activation (Scheme 28).[45] The reaction platform was also amendable to the generation of γ-substituted bicyclic lactones by including an olefin coupling partner to effect a second C(sp^2)–H activation event. Density functional theory (DFT) calculations were performed to

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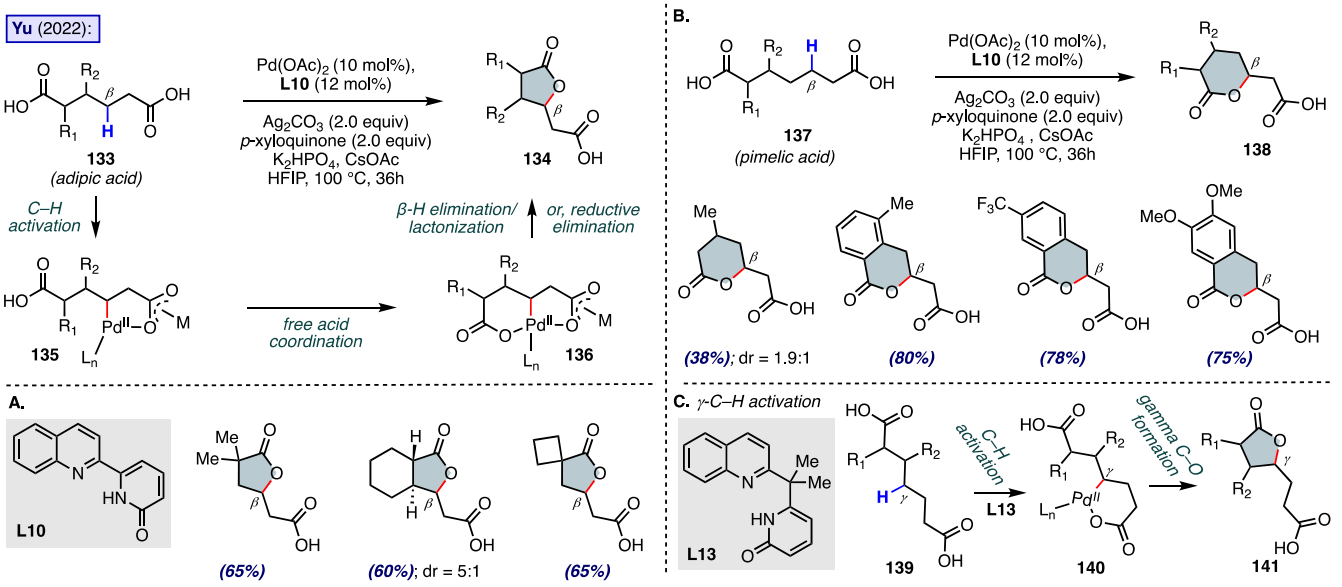
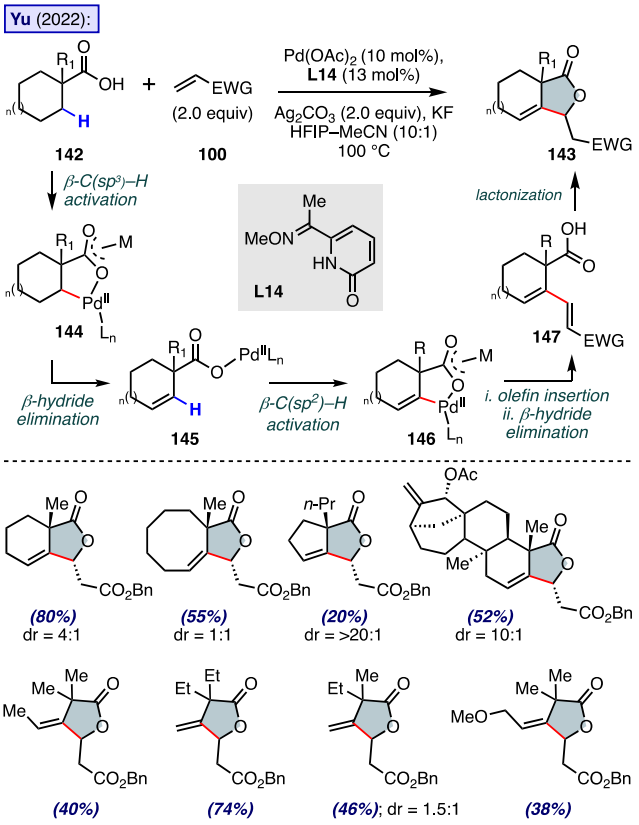
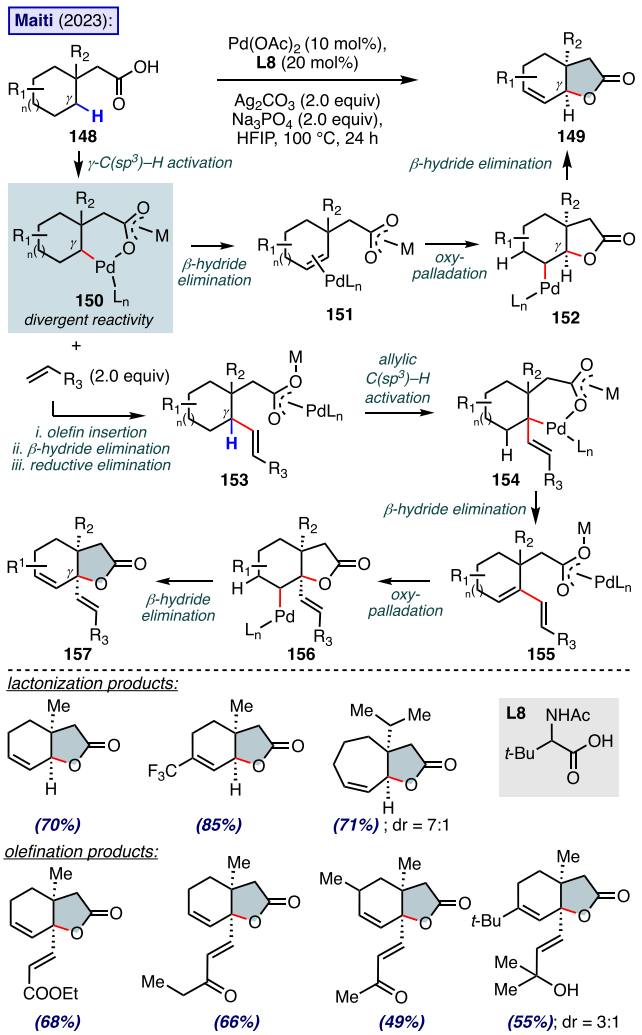
Scheme 26. Site-Selective Methylene C−H Activation of Dicarboxylic Acids Enables Complex Lactone Synthesis



Scheme 27. Tandem Dehydrogenation−Olefination−Lactonization Reaction Offers a One-Step Synthesis of β-Alkylidene-γ-lactones



Scheme 28. Synthesis of Unsaturated Bicyclic Lactones via an Initial Methylene C(sp^3)−H Bond Activation



develop a deeper understanding of the operating mechanism. Following the initial γ-C(sp^3)−H activation, the resulting palladium bicyclic intermediate **150** could undergo divergent reactivity to either give rise to the direct lactonization products or participate in an olefin insertion reaction. For the lactonization products, the palladacycle **150** is subject to a β-hydride elimination and oxypalladation event to provide a

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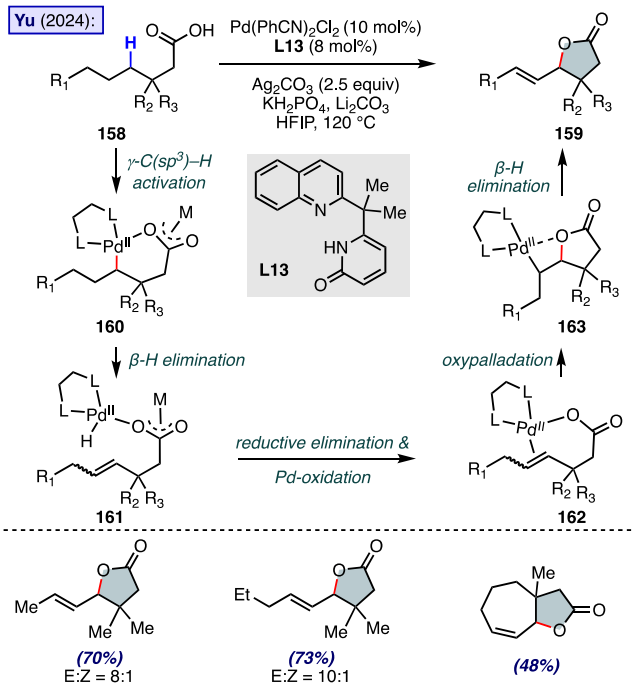
palladated γ-lactone **152**. A second β-hydride elimination event generates the dehydrogenated γ-lactone products **149**. For the olefination products **157**, the ini-tial palladacycle **150** reacts with an olefin via olefin insertion followed by β-hydride elimination and reductive elimination to generate the γ-olefinated intermediate **153**. At this stage, an allylic C(sp^3)−H activation forms a second palladacycle **154** and ensuing β-hydride elimination and oxypalladation provide the palladated γ-substituted lactone **156**. A final β-hydride elimination yields the γ-substituted lactonization products **157**. The scope of both reaction pathways was investigated. The lactonization and dehydrogenation proceed efficiently on β-substituted aliphatic acids, providing bicycles with varying ring sizes and substituents in up to 85% yield. Similar substrates were applied to the synthesis of γ-olefinated lactones, where a variety of electron deficient olefins in moderate to high yields. Notably, primary and secondary allylic alcohols could also be employed to obtain products where the alcohol is oxidized, and a tertiary alcohol coupling partner was also well tolerated, providing the tertiary alcohol product in 55% and 3:1 dr.

In 2024, the Yu lab reported a catalyst controlled γ-C(sp^3)−H lactonization reaction that was able to selectively differentiate between methyl and methylene C−H bonds (Scheme 29).[40] Their efforts toward the γ-methyl C−H bond activation

Scheme 29. Synthesis of Vinyl γ-Lactones via a Methylene C−H Bond Activation

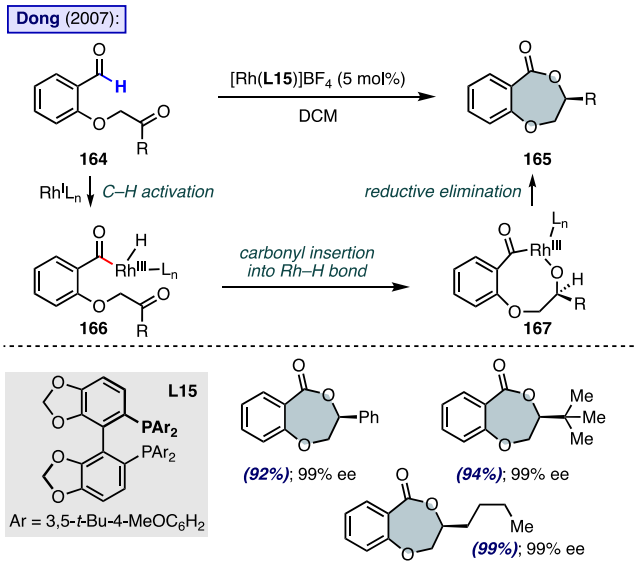


was previously discussed; however, the authors also developed alternative set of conditions toward chemoselective activation of γ-methylene C−H bond that resulted in effective preparation of γ-lactones neighboring to a new olefin functionality (Scheme 29). The authors were able to accomplish this reactivity switch by employing the six-membered quinoline−pyridone ligand **L13**. The authors postulate that selective γ-methylene C−H activation is followed by a β-hydride elimination (**160**→**161**). Subsequent lactonization via oxypalladation reaction of the pendant carboxylic acid group on to the olefin (**162**→**163**) generates the cyclopalladated **163** which upon a second β-hydride elimination event provides the vinyl γ-lactone products **159**. The newly formed alkene is formed with great E/Z selectivity and delivers a powerful synthetic handle for additional product diversification chemistry.

6. SYNTHETIC ACCESS TO LACTONES VIA ACTIVATION OF AN ALDEHYDIC C−H BOND

Aside from the more common functionalization of alkyl and aryl C−H bonds, another strategy toward efficient lactone synthesis could involve a metal catalyzed activation of an aldehydic C−H bond. In 2007, Dong and co-workers disclosed an enantioselective rhodium-catalyzed cyclization reaction capable of affording the synthesis of seven-membered lactones in excellent yields and with high enantiomeric excess (Scheme 30).[46] Their strategy relied on the use of cationic Rh(I)

Scheme 30. Rhodium-Catalyzed Aldehydic C−H Bond Activation Enantioenriched Seven-Membered Lactones



catalyst in combination with an electron-rich chiral biphenyl-phosphine ligand **L15**. Mechanistically, this transformation is believed to proceed via an initial C−H activation of the aldehyde forming the acyl-Rh(III)-hydride intermediate **166**. Subsequent reversible insertion of the pendant carbonyl moiety into the Rh−H bond generates the rhodacycle **167** that upon reductive elimination furnishes the lactone product **165** and regenerates the Rh(I) catalyst. The scope of this transformation included several aliphatic α-alkoxy ketone substrates of varying lengths that were transformed to the corresponding lactones with high efficiency >85% yield and excellent enantioselectivities (>99% ee)

Additional effort in this area by the same group resulted in a novel diastereodivergent synthesis of γ-lactones via an enantioselective C−H activation of aliphatic aldehydes. Dong and co-workers found that a shrewd combination of a rhodium catalyst with JoSPOphos ligand (**L16**) is capable of accessing both *anti*- and *syn*-γ-lactone diastereomers from 4,4′-diketo aldehyde substrates **168** (Scheme 31).[47] Specifically, it was discovered that the *anti*-diastereomer **169** was favored in polar aprotic solvents, such as 1,2-dimethoxyethane (DME) and the *syn*- diastereomer **170** could be obtained with a protic *tert*-amyl alcohol as the solvent in combinations with appropriate

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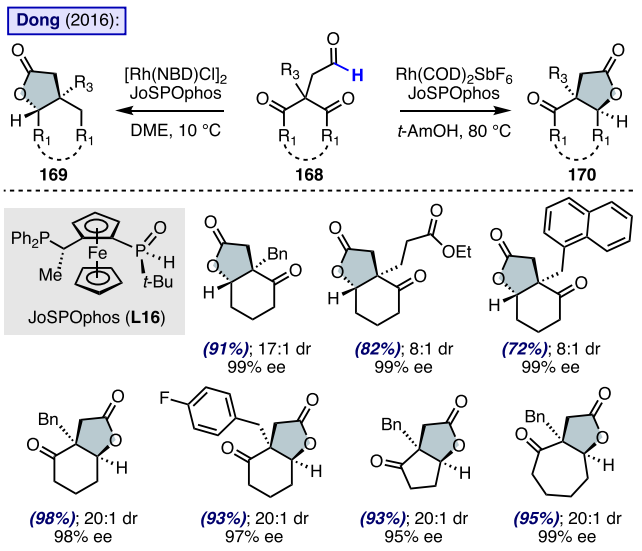
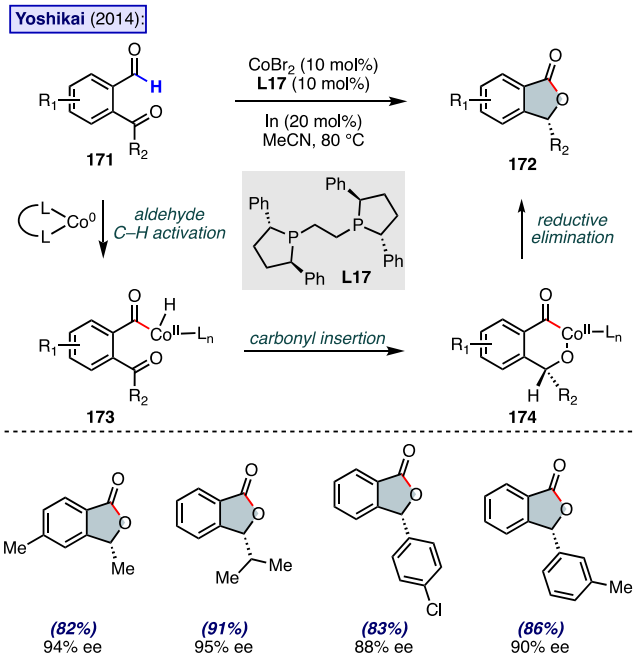
Scheme 31. Diastereoselective Lactone Synthesis via C−H Bond Activation of Aliphatic Aldehydes Employing a Rhodium Catalyst



rhodium catalyst counterions. This powerful lactonization is believed to proceed through an analogous reaction mechanism to the one described above which was verified with crossover and KIE experiments. A variety of γ-lactones could be prepared bearing a large array of alkyl/aryl groups and with a varying number of carbon atoms in the central ring system. These lactones were all obtained in overall high yields (53−98%), high diastereoselectivities (6−17:1 dr) and with excellent enantioselectivities.

Yang and Yoshikai reported a catalytic addition of an aldehyde C−H bond across a pendant ketone group, resulting in the formation of the corresponding lactone product using a cobalt−chiral phosphine catalytic system (Scheme 32).[48] In this 2014 publication, the authors identified that a combination of cobalt(II) bromide and the bidentate ligand (−)-1,2-bis((2*R*,5*R*)-2,5-diphenylphospholano)ethane provided high yields of the desired products **172** in an enantioselective manner. Mechanistically, the reaction is proposed to proceed via initial C−H activation of the aldehyde by a cobalt(0) species, generated in situ through reduction with indium powder. The resulting cobalt(II) complex **173** then undergoes carbonyl insertion to form a six-membered metallacycle **174**, which upon reductive elimination delivers the lactone product **172** with high enantioselectivity. This methodology enabled the synthesis of a wide array of lactone products, accommodating diverse substitution patterns on both the aromatic ring and the α-position of the carbonyl group.

Scheme 32. Cobalt-Catalyzed Enantioselective Hydroacylation of Ketones to Prepare Lactone Products

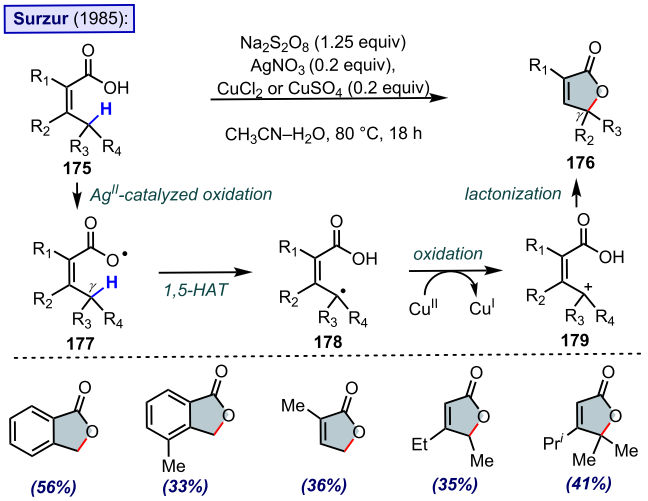


7. ONE-ELECTRON C(SP^3)−H FUNCTIONALIZATION REACTIONS TO SYNTHESIZE LACTONES

Lactonizations via one-electron C−H functionalization frequently utilize hydrogen atom transfer pathways and substrate preorganization to enable selective oxidative cyclization. Moreover, transition metal catalysts capable of accessing multiple oxidation states in combination with finely tuned ligands have been shown to generate a variety of oxygen- and carbon-centered radicals, leading to effective formation of numerous interesting lactone scaffolds. In the following section, we summarize advancements in one-electron C-(sp^3)−H lactonization reactions, from early discoveries of reactivity to the enantioselective functionalization of unactivated C−H bonds.

Lactonization via catalytic one-electron C−H functionalization was accomplished as early as 1985 by Surzur and coworkers (Scheme 33).[49] They demonstrated that γ-lactones

Scheme 33. Lactonization of Acrylic Acids Enabled by Copper and Silver Catalysts



176 could be synthesized from acrylic acids using copper and silver catalysts. Mechanistically, following oxidation of the acrylic acid with silver(II), the oxygen-centered radical in **177** undergoes an intramolecular 1,5−hydrogen atom transfer reaction to generate an allylic carbon-centered radical **178**. This intermediate can then be oxidized with copper(II) to yield a carbocation **179** that can subsequently react with the free acid oxygen to yield the α,β-unsaturated lactone product **176**. Six examples were reported including substituted

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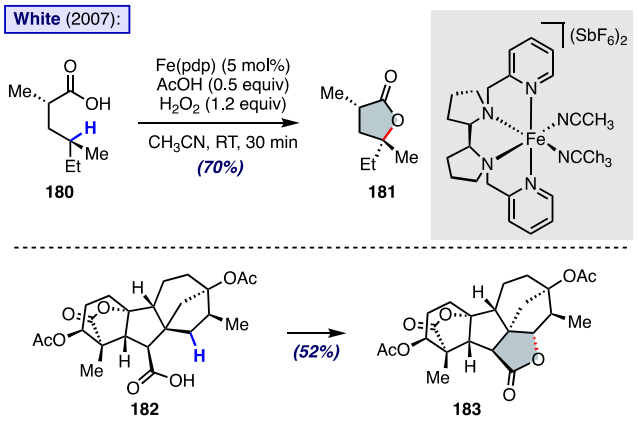
benzylphthalides and furanones that were produced in moderate 33−56% yield.

White and co-workers reported an innovative, bioinspired iron catalyst with a pdp (pdp = 2-[[2-(1-(pyridin-2-ylmethyl)-pyrrolidin-2-yl)pyrrolidin-1-yl]methyl]pyridine) ligand to perform γ-lactonization of aliphatic carboxylic acid substrates via C−H hydroxylation in 2007 (Scheme 34).[50] In their pioneering report, a directed C−H oxidation reaction of hexanoic acid generated the γ-disubstituted lactone **181** in 70% yield. The authors immediately demonstrated the impact of their chemistry for the derivatization of complex molecules by performing a directed hydroxylation and lactonization of a tetrahydrogibberellic acid analog **183** in 52% yield.

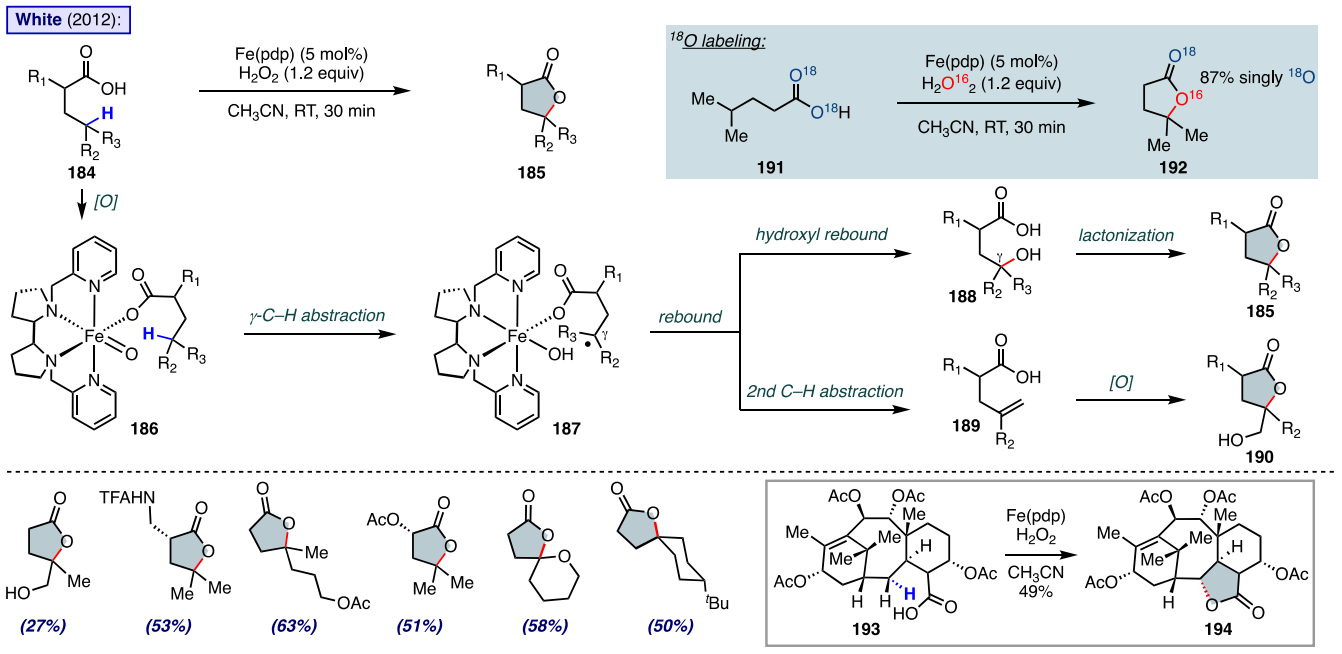
Scheme 34. Lactonization via C−H Oxidation with an Iron-Based Small-Molecule Catalyst



White's subsequent report in 2012 provided further investigation into the substrate scope and reaction pathway (Scheme 35).[51] Mechanistically, following coordination and oxidation of the iron complex by hydrogen peroxide, a one-electron γ-C−H abstraction generates a carbon-centered radical **187**. This intermediate can then lactonize via two possible pathways: *i.* hydroxyl rebound from the iron complex that installs a hydroxy group at the γ-position (**188**) that can undergo spontaneous nucleophilic lactonization to form **185** or *ii.* a second C−H abstraction event to generate a desaturated intermediate **189** followed by oxidative intramolecular cyclization with the pendant carboxylic acid group to yield the hydroxy-lactone products such as **190** that are frequently reported by the authors as minor products. ^{18}O labeling studies with the substrate **191** and normal hydrogen peroxide support that the hydroxyl rebound mechanism is the predominant pathway with 87% of the nonhydroxy lactone product **192** being singly ^{18}O-labeled. Subsequent mechanistic work and calculations have been used to characterize the putative iron(V) oxo complex and corroborate the hydroxyl rebound mechanism.[52] A variety of γ-disubstituted lactone products bearing pendant aliphatic and electron-withdrawing functionality were prepared in moderate yields ranging from 27−65%. Additionally, the synthetic utility of this C−H lactonization protocol was demonstrated via the C−H hydroxylation and lactonization of the B ring of the taxane derivative **193** that provided the product **194** in 49% yield.

Later in 2020, Costas utilized a manganese complex with a similar ligand and peroxide to affect the enantioselective γ-C(sp^3)−H hydroxylation/lactonization of methylenes (Scheme 36).[53] An analogous mechanism of γ-C(sp^3)−H activation followed by hydroxyl rebound or carboxylate rebound is presumed to be operative. Detailed mechanistic calculations suggest that the γ-(Csp^3)−H activation occurs via 1,7-HAT and isotope labeling studies with the bis-^{18}O-labeled substrate **203** provided the doubly labeled product **204** in 50% yield, suggesting that both rebound pathways are viable. The group also observed variation in the major product outcome (**196**−**198**) based on the choice of ligand when using unsymmetrical substrates containing competitive proximal and distal methylenes. A scope of adamantane-carboxylic acids was surveyed and provided varying ratios of differentially

Scheme 35. Aliphatic C−H Hydroxylation with an Iron Catalyst and Hydrogen Peroxide



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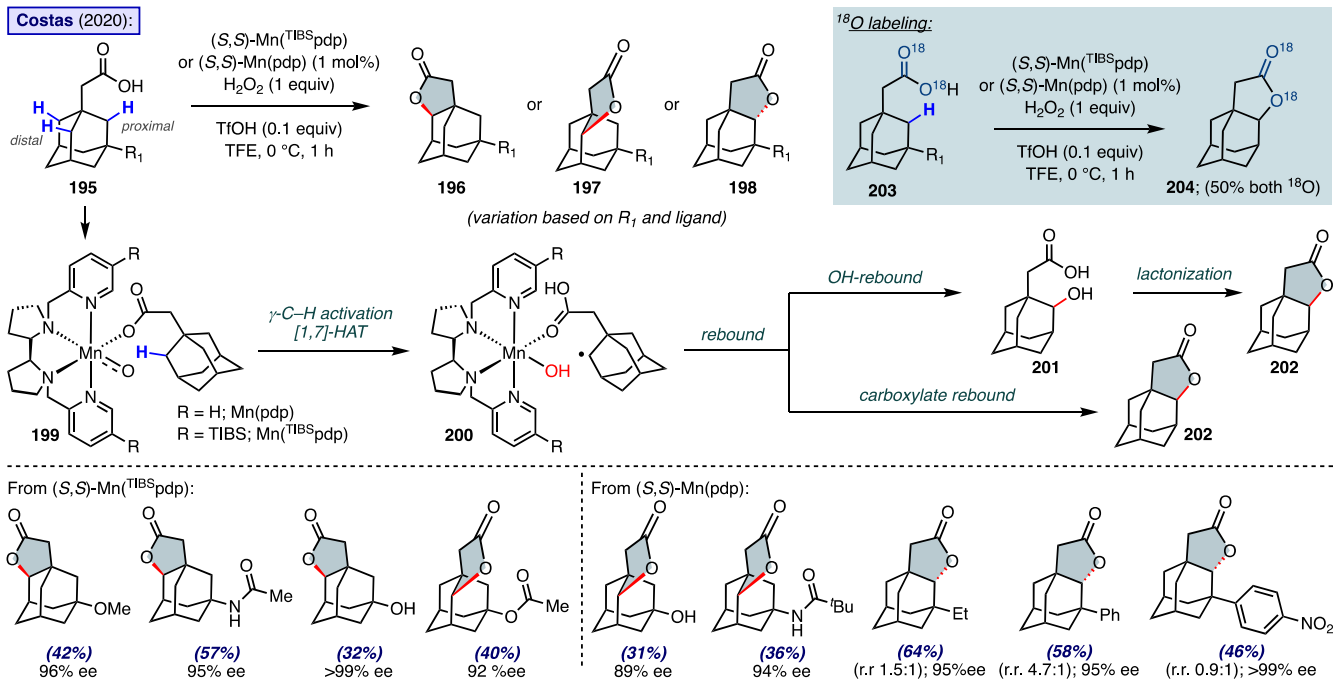
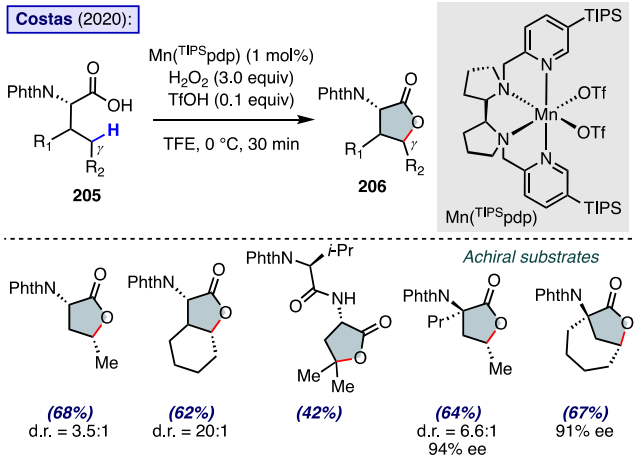
Scheme 36. Site-Selective Lactonization of Carboxylic Acids by a Sterically Encumbered Manganese Catalyst



activated. The major products were isolated in 23−65% yield in moderate regioselectivities.

The same year, the group reported that the manganese ^{TIPS}-pdp catalyst could also be employed to perform carboxylate-directed γ-C(sp^3)−H activation of α-amino acid methylenes (Scheme 37).[54] They surveyed a variety of proteinogenic and

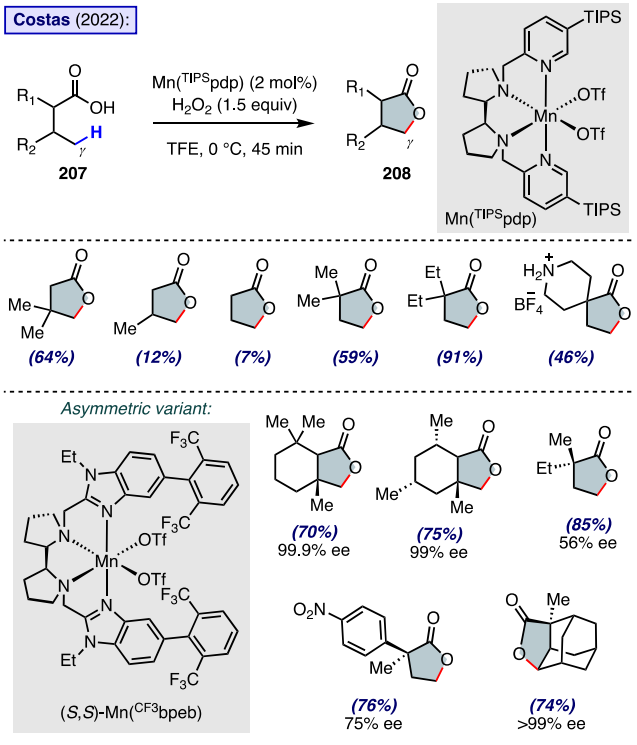
Scheme 37. γ-C−H Lactonization of α-Amino Acids Using a Manganese Catalyst



nonproteinogenic amino acids bearing aliphatic substituents which provided γ-lactones in up to 85% yield and moderate to high diastereoselectivities. Notably, the authors also showed that applying their conditions to achiral amino acids can generate unique lactone products with five examples isolated in >90% ee.

Costas and co-workers extended their methodology to the γ-C(sp^3)−H hydroxylation/lactonization of methyl groups in 2022 (Scheme 38).[55] Using similar conditions and the manganese TIPS-pdp complex, simple α- or β- disubstituted

Scheme 38. γ-Lactones via Methyl Group Hydroxylation and Subsequent Lactonization Employing a Manganese Catalyst



aliphatic acid substrates **207** could efficiency form the desired lactones **208** in up to 91% yield. Removing steric bulk significantly decreased the yield to as low as 7% for butyric acid, but the reaction proved tolerant of notable functionality such as secondary amines to form unique spiro-heterocycles. Costas and co-workers extended the methodology to the asymmetric preparation of lactones through modification of

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the pyridine donors in the manganese complex to *N*-ethylbenzimidazoles.[56] A variety of aliphatic carboxylic acid substrates could be converted to chiral lactone products in excellent yields and up to 99.9% ee, providing a privileged entry into chiral scaffolds from simple starting materials. The same year, Bryliakov and co-workers reported that similar manganese complexes could be used to access racemic mixtures of γ- and δ-lactones from fatty acid substrates.[57]

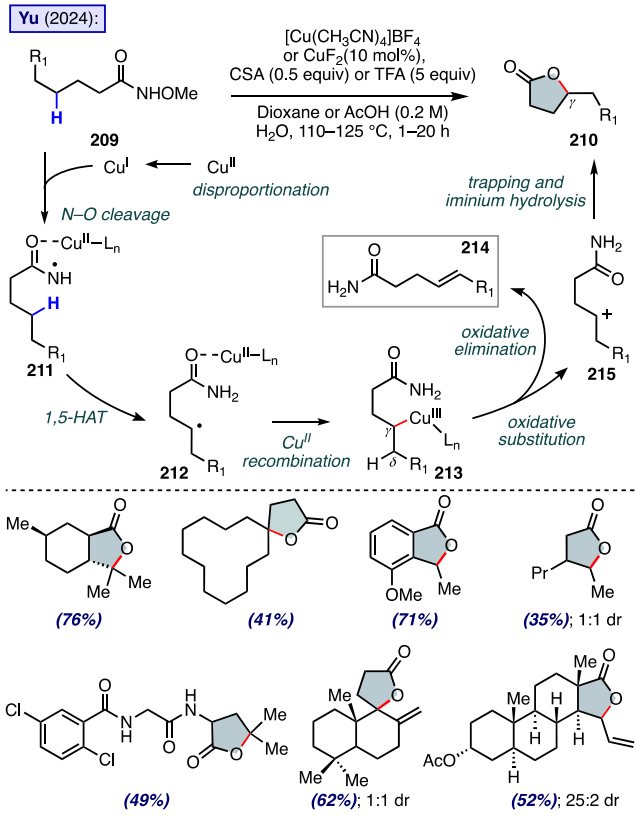
Yu and co-workers reported two one-electron γ-C(sp^3)−H lactonizations of methylenes in 2024 (Scheme 39).[58] In the first report, *N*-methoxyamides **209** could be transformed into aliphatic γ-lactones **210** through a selective C−H abstraction of the γ-position. In the mechanistic pathway proposed by the authors, the copper(II) precatalyst first forms the active copper(I) catalyst via disproportionation. This Cu(I) species then reacts with the amide substrate to generate a nitrogen-centered radical via an N−O bond cleavage (**209**→**211**). The resulting radical **211** performs a 1,5-HAT step to produce a secondary carbon-centered radical **212** that undergoes recombination with copper(II) to form an alkylcopper(III) species **213**. The authors found that the highly reactive intermediate **213** exhibits divergent reactivity and can form two different products **214** and **215**. In order to form the desired lactone products **210**, acidic and aqueous reaction conditions were found to be optimal for generating the γ-lactones via an oxidative substitution pathway (**213**→**215**) and subsequent carbocation trapping and iminium hydrolysis.

When the authors slightly modified their reaction conditions and included the addition of 8-methoxyquinoline as the ligand, the alkylcopper(III) species **213** underwent an oxidative elimination pathway, thereby, generating the corresponding desaturated acyclic product **214**. In detail, a series of aliphatic and aromatic *N*-methoxyamides were successfully converted to γ-lactones in up to 78% yield. Generally, γ-disubstituted products were formed the most efficiently, correlating with the corresponding intermediate tertiary radical and carbocation stability. The reaction conditions were also amenable to providing complex products containing peptide bonds as well as complex aliphatic scaffolds such as terpenes and steroids.

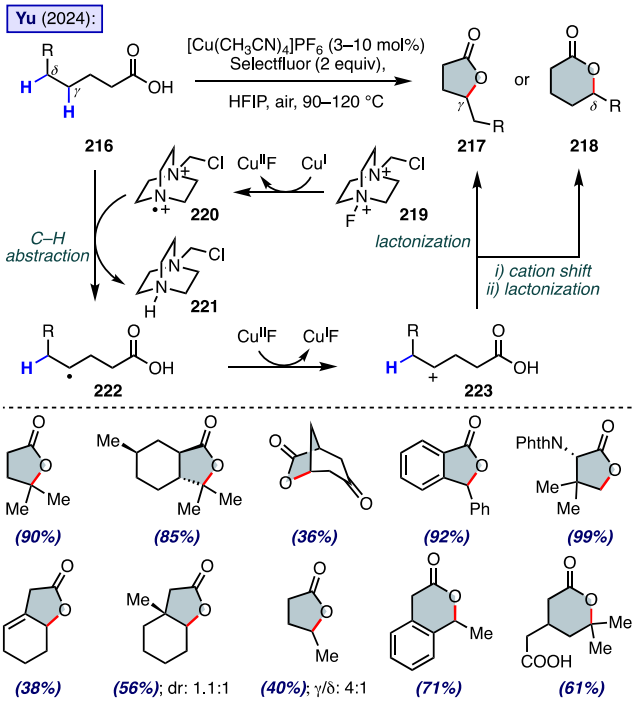
Later the same year, the same group reported another copper-catalyzed C−H functionalization of γ-C−H bonds to produce γ- or δ-lactones directly from aliphatic carboxylic acids using a copper catalyst and Selectfluor (**219**) as the oxidant (Scheme 40).[59] In this lactonization reaction, copper(I) is first oxidized by the Selectfluor which results in a generation of a nitrogen-centered radical cation (**219**→**220**). Next, an electrophilic HAT forms a carbon centered radical **222**, that is subsequently oxidized by the copper(II) species to access the secondary carbocation **223**. This can then undergo intramolecular lactonization step to produce the five-membered γ-lactones **217**, or in the case of some substrates possessing δ−C-H bonds, a carbocation shift followed by lactonization is proposed to generate the six-membered δ-lactones **218**. The reaction proved compatible with primary, secondary, tertiary, allylic, methylene and benzylic γ-C−H bonds and generated the products in up to 99% in the case of phthalimide protected *tert*-leucine. While the majority of substrates exclusively formed the γ-lactones **217**, the δ-lactones **218** could be produced in up to 71% yield in the case of 2-ethyl phenylacetic acid.

Biocatalytic processes have historically drawn inspiration from one-electron C−H lactonizations, suggesting that modern advances in biocatalysis would be able to be used to prepare lactones in high levels of regio and enantioselectivity.

Scheme 39. Redox-Neutral C−H Lactonization of *N*-Methoxyamides with a Copper Catalyst



Scheme 40. Copper-Catalyzed γ-C(sp^3)−H Lactonization of Aliphatic Carboxylic Acids Enables Efficient Lactone Synthesis



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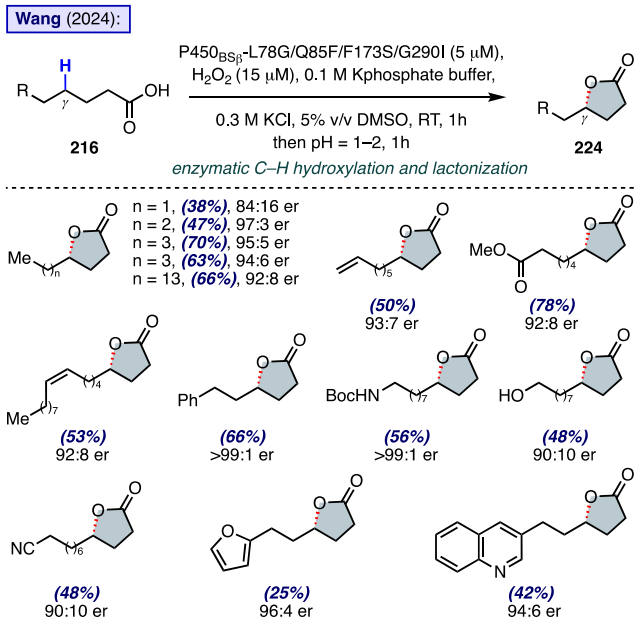
Biocatalytic C(sp^3)−H lactonization was reported as early as 2019 by Flitsch and co-workers via the δ-C−H hydroxylation of decanoic acid and subsequent formation of the six-membered lactone by the cytochrome P450 enzyme P450-TT.[60] In an impressive advance, the Wang group expanded the scope of biocatalytic C−H lactonization of carboxylic acids in 2024 via the directed evolution of a cytochrome P450 enzyme (Scheme 41).[61] Four rounds of directed evolution led to the

Scheme 41. Biocatalytic Enantioselective Lactonization of Inactivated γ-C(sp^3)−H Bonds of Aliphatic Carboxylic Acids



discovery that the quadruple mutant L78G/Q85F/F173S/G290I capable of providing the γ-C−H hydroxylated products in high yields with excellent regioselectivity control. Analogous to early work with bioinspired iron catalysts, these enzymes utilize a reactive iron(IV)-oxo heme complex to perform a C−H abstraction of the carboxylic acid substrates followed by a hydroxyl rebound. Subsequent treatment with aqueous acid leads to the formation of the enantiopure lactone products **224**. Studies on the crystal structure revealed that the selectivity arises from the positioning of the γ-carbon closest to the iron heme complex, inducing a favorable positioning for selective γ-oxidation (PDB ID 8HKD). The mutant enzyme successfully transformed 6 to 18 chain carboxylic acids to the corresponding γ-lactones in synthetically useful yields (38−70%) and enantioselectivities ranging from 84:16 to 97:3. Additionally, an impressive array of functional groups was tolerated including unsaturated carbon−carbon bonds, esters, aromatics, amines, hydroxyls, nitriles and halogenated compounds, underscoring the power of enzymes to address synthetic challenges.

8. APPLICATIONS IN COMPLEX MOLECULE SYNTHESIS

The field of total synthesis has indisputably benefited from the remarkable achievements of modern C−H activation methodologies, which enable the selective functionalization of traditionally inert and inherently unreactive C−H bonds. Particularly valuable are methods that selectively decorate these positions without requiring the installation and removal of exogenous directing groups, thereby minimizing non-strategic transformations in a total synthetic sequence.[62] In the context of C−H lactonization reactions, numerous examples of carboxylic acid- or amide-directed C(sp^2)−H and C(sp^3)−H activation and lactonization offer synthetic chemists a diverse toolkit for constructing relevant and complex lactone-containing scaffolds. In this section, we highlight several key examples of transition metal-catalyzed C−H lactonization methods that directly enable the synthesis of complex natural products. These examples underscore the importance of multifunctional group tolerance, site selectivity within intricate scaffolds and will hopefully encourage further adoption of these strategies in complex synthesis.

In 2009, Stang and White reported a total synthesis of the macrolide polyketide 6-deoxyerythronolide D (**80**) featuring a late-stage allylic C−H lactonization reaction (Scheme 42).[29] In their approach, they first synthesized the linear precursor **225** using a series of stereoselective reactions in an iterative fashion and in an 18% overall yield. The key intramolecular C−H macrolactonization reaction of **225** provided the allylic lactone **226** in combined 56% yield based on two subjections of the substrate to the reaction conditions. This powerful transformation rapidly formed the desired macrolide scaffold and allowed them to complete the synthesis of **80** in only three additional steps. Mal and co-workers utilized carboxylic acid directed C(sp^2)−H alkylation to prepare a key phthalide intermediate in their synthesis of Arnottin I (**230**).[63] Their approach required them to access the lactone **228** which was achieved in one step by treatmeant of **227** with dibromomethane in the presence of palladium acetate in 78% yield. Subsequent lithium bis(trimethylsilyl)amide mediated annulation between the lactone **228** and **229** provided the natural product in a total of three steps relative to the longest linear sequence, underscoring the potential of C−H activation strategies to give remarkable and efficient access to complex chemical scaffolds.

(−)-Berkelic acid (**234**) is a structurally complex tetracyclic natural product isolated from the Berkeley Pit Lake in Montana that has attracted considerable attention from the synthetic community due to its uniquely functionalized skeleton and potent bioactive properties. Wang and co-workers employed a Pd(II)-catalyzed C(sp^2)−H alkylation reaction with an epoxide to generate a direct access to the isochromane skeleton of **233**.[64] In their approach, the authors first prepared the *N*-methoxybenzamide **231** and used palladium acetate, potassium acetate and copper(II) chloride in the presence of epoxide **232** that provided the desired lactone product **233** in 86% yield on gram scale. Using this strategy, Wang and co-workers obtained (−)-Berkelic acid (**234**) in 11 steps and in 13.9% overall yield.

Another elegant example of C−H lactonization in complex molecule synthesis was reported by Snyder and co-workers en route to a family of complex secondary metabolites termed scaparvins.[65] These molecules were isolated from the epilithic liverwort *Scapania parva* Steph. and possess a distinct cage-like structure with a characteristic intramolecular ketal moiety. Snyder and co-workers' approach hinged on their ability to perform a key late-stage C−H functionalization reaction that would convert a carboxylic acid group within substrate **235** to a lactone by a selective oxidation of a proximal tertiary C−H bond. This was accomplished by exposure of **235** to an Fe(pdp) catalyst in the presence of H_2O_2 which provided the

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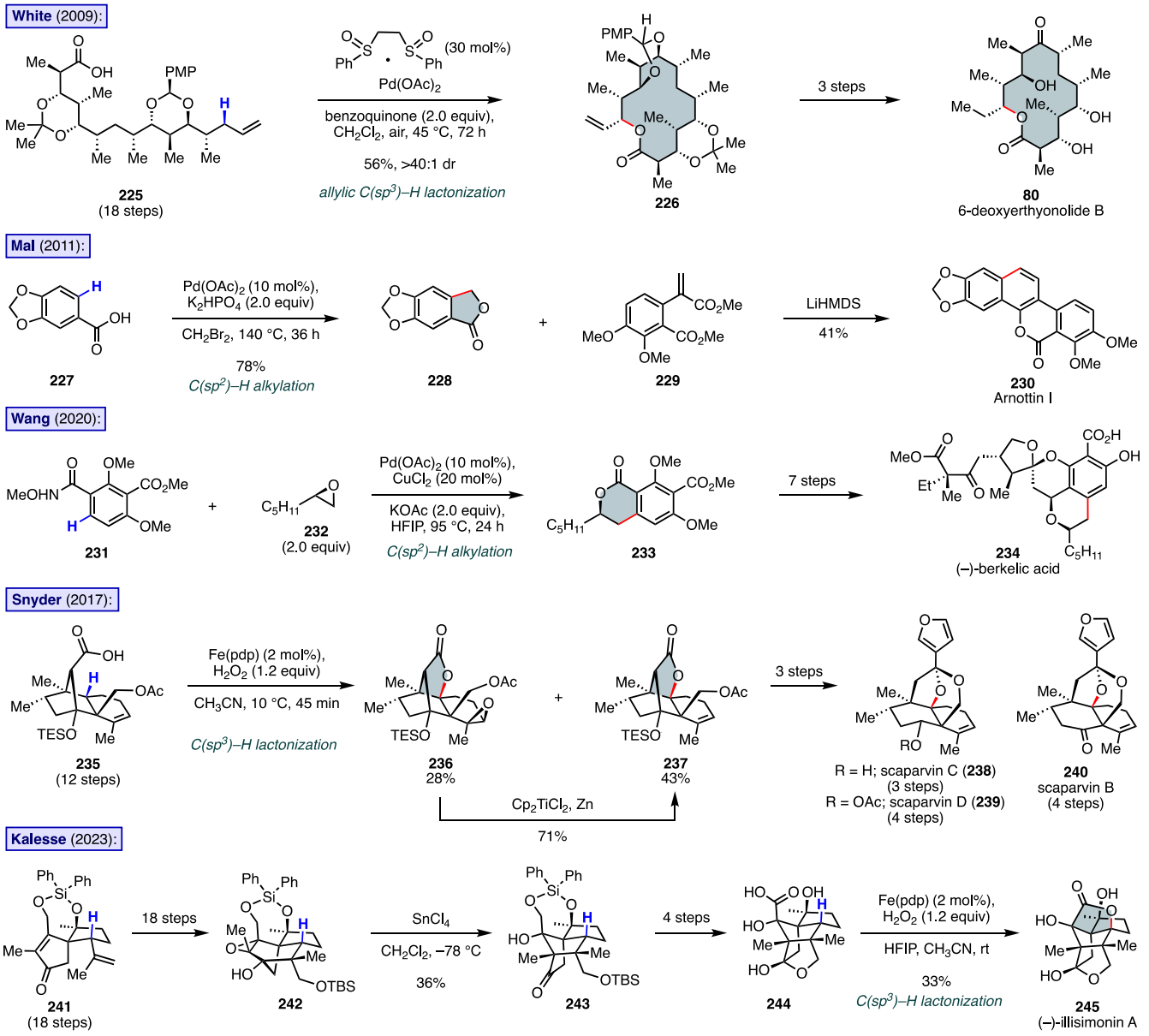
Scheme 42. Synthesis of Complex Natural Products Enabled by C−H Lactonization Reactions



desired lactone product **237** in 43% yield along with 28% of an epoxide **236**. Moreover, the epoxide side product could be readily recycled to the lactone **237** in 71% yield by treatment with titanocene dichloride and zinc. With the desired lactone compound **237** at hand, the authors were able to complete the synthesis of three different scaparvins.

A similar key C(sp^3)−H activation step using an Fe(pdp) and H_2O_2 catalyst system was utilized in the enantioselective synthesis of (−)-illisimonin A by the Kalesse group in 2023.[66] In their route, the spirocyclic siloxane **241** was accessed in 18 steps from geraniol. In 18 transformations, **241** was elaborated to the tricyclic epoxide **242** that undergoes a key semipinacol rearrangement (tin tetrachloride) to afford the desired diastereomer of **243**. In four steps, the α-hydroxy carboxylic acid **244** was obtained as the substrate for the (Csp^3)−H activation of the γ-methine. The lactonization reaction directly affords the natural product **245** in 33% yield, highlighting the potential of C−H activation as a powerful strategy for the elaboration of late-stage, complex molecules with numerous unprotected positions.

9. CONCLUSIONS

Advancements in C−H activation have modernized lactone synthesis from highly prefunctionalized substrates and forcing conditions to elegant transformations of simple acids, amides, or aldehyde substrates. The judicious determination of ligand and reaction conditions enable these modern approaches to deliver regio- and diastereoselective product outcomes. Decades of research into transition metal-catalyzed two-electron C−H activation and functionalization of C(sp^2)−H and C(sp^3)−H bonds have facilitated the construction of increasingly complex aromatic and aliphatic lactones. Developing an understanding of the operative reaction mechanisms and intermediates has empowered chemists with the ability to extend these reaction pathways to coupling reactions with diverse partners, such as epoxides, halocarbons, olefins and alkynes. Similarly, the exploration of one-electron C−H

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functionalizations has driven advancements in transition metal-catalyzed C−H hydroxylation via synthetic and biocatalytic methods to achieve regio- and enantioselective lactone preparations. Showcasing these lactonization approaches along with practical synthetic applications underscores the vast chemical space that can be accessed via modern C−H functionalization methods and will undoubtedly inspire further developments in this area of synthetic chemistry.

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Notes

The authors declare no competing financial interest.

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