

The Direct Pd-Catalyzed γ -Lactonization of Aliphatic Carboxylic Acids

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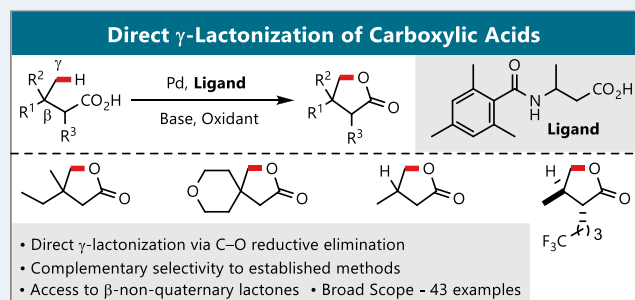
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ABSTRACT: A direct palladium-catalyzed γ -lactonization of free carboxylic acids via C–O reductive elimination as a key step is described. Notable aspects of this protocol include the use of convenient and easily available sodium percarbonate as an oxidant and the development of a highly efficient β -alanine-derived ligand. The reported method enables the functionalization of a wide range of aliphatic acids including previously inaccessible β -non-quaternary acids. The regioselectivity and consequently substrate scope of this protocol proved complementary to established routes for the direct lactonization of aliphatic carboxylic acids. Through this report, a valuable compound library of γ -lactones with potential applications in various fields has become available.

KEYWORDS: γ -lactonization, carboxylic acids, Pd-catalysis, C–H activation, ligand design



INTRODUCTION

γ -Lactones serve as versatile synthetic intermediates in organic synthesis and represent an important scaffold that finds applications in various fields including bioactive natural products, flavors, perfumes, and pharmaceuticals (Scheme 1A).^{1,2} While traditional functional group interconversion approaches,^{1,3} such as halolactonization and intramolecular cyclization, provide access to γ -lactones, their reliance on prefunctionalized starting materials constitutes a major drawback in terms of step and atom economy. A straightforward and attractive alternative is to access γ -lactones directly from the respective carboxylic acids (Scheme 1B). Such transformations bear the potential for a rapid buildup of molecular complexity, giving access to compound libraries in a single step from readily available starting materials. In this context, transition-metal-catalyzed C–H functionalization reactions have been identified as a highly promising tool, and several transition-metal-based methods with distinct mechanistic pathways have been developed: (i) The homolytic cleavage of C–H bonds with 3d metals^{4–12} or enzymes¹³ via a hydrogen atom transfer (HAT) event enables lactonizations in which the reactivity and regioselectivity is governed by the bond dissociation energies (BDEs) of the respective C–H bonds (Scheme 1B, Path A). (ii) The desaturation of carboxylic acids through a methylene C–H bond activation followed by β -hydride elimination in conjunction with a cyclization by addition of the carboxylic acid to the newly formed double bond has enabled lactone syntheses (Scheme 1B, path B), although it should be noted that the intermediate desaturation imposes some limitations on the structural variability of lactones accessed through this

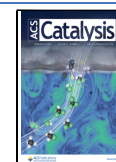
approach.^{14,15} (iii) The formation of cyclometalated intermediates via the activation of activated benzylic^{16–18} or allylic C–H bonds¹⁹ and a subsequent lactonization, which has been proposed to occur via an S_N -like displacement²⁰ (Scheme 1B, path C). (iv) The use of substrates bearing additional directing groups^{21,22} or having a suitably placed internal nucleophilic functional group capable of intercepting a catalytic cycle.²³ Although these protocols have remarkably advanced the current state of the art, one highly attractive alternative pathway has remained out of reach: A widely applicable direct C(sp³)–H activation of unactivated γ -C(sp³)–H bonds followed by a C–O reductive elimination (C–O RE), which is expected to display a regioselectivity pattern complementing the above-mentioned existing approaches giving access to a currently inaccessible lactone spectrum (Scheme 1B, path D). Previous studies toward this goal have remained limited by the use of an expensive platinum catalyst and a narrow range of substrates.^{24,25} Considering the fact that the C–O RE constitutes a fundamental challenge in organometallic chemistry,^{26–28} we became interested in developing a protocol which would harness the weak directing ability of the carboxylate unit to activate the terminal γ -C(sp³)–H bonds of simple acyclic acids and allow for the subsequent C–O reductive elimination to deliver the

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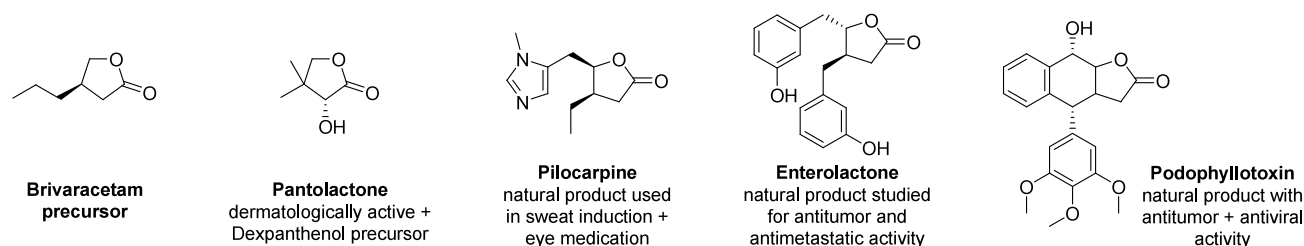
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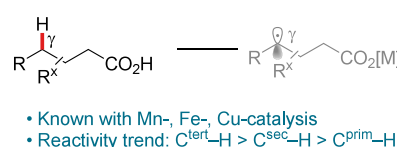
Scheme 1. (A) Importance of γ -Lactones as Bioactive Compounds and Versatile Synthetic Intermediates; (B) C–H Oxidation of Carboxylic Acids as Ideal Synthetic Approach to γ -Lactones—Literature Precedent and Aim of This Work

A. Importance of γ -Lactones as Bioactive Compounds and Versatile Synthetic Intermediates

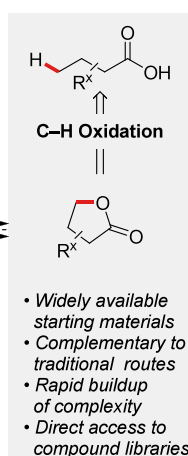
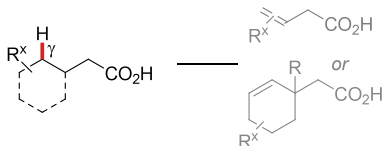


B. C–H Oxidation of Carboxylic Acids as Ideal Synthetic Approach to γ -Lactones - Literature Precedent and Aim of This Work

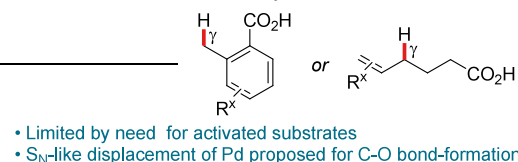
Path A: Oxidation via Hydrogen Atom Transfer (HAT)



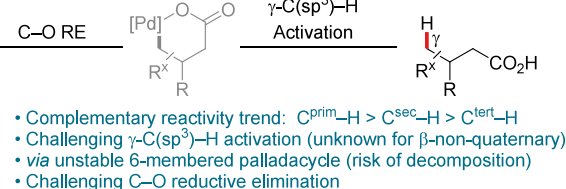
Path B: Lactone Synthesis via Desaturation



Path C: Lactone Synthesis via Activated C–H Bonds



Path D: Lactone Synthesis via C–O Reductive Elimination (RE) – This Work

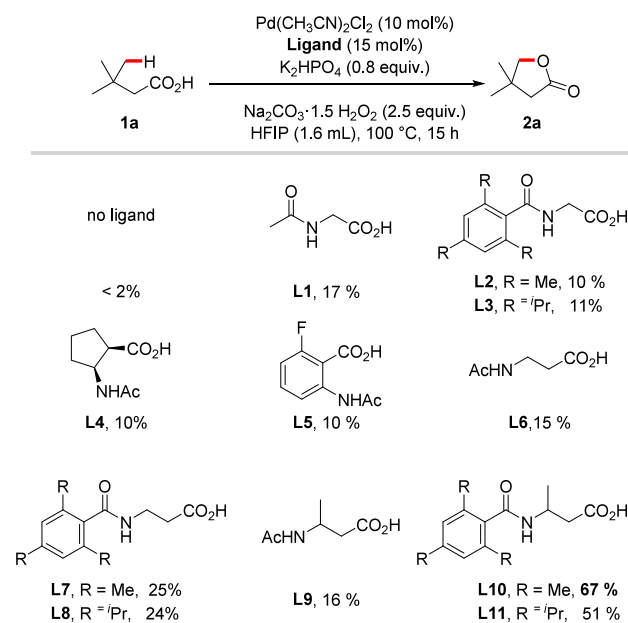


desired products.²⁹ In addition to the existing fundamental challenges^{30–33} associated with the C–H activation step, we considered that the stability of the cyclopalladated intermediate generated upon $\gamma\text{-C}(\text{sp}^3)\text{-H}$ activation would be one of the key factors influencing the feasibility of the subsequent C–O RE step. This would be particularly challenging in the case of the six-membered palladacycles generated upon $\gamma\text{-C}(\text{sp}^3)\text{-H}$ activation from β -non-quaternary acids, which are prone to decomposition,³⁴ for example, via a β -hydride elimination competing with the C–O RE step. Based on our experience and recent advances in high-valent palladium-mediated carbon-heteroatom bond formation reactions,^{32,35,36} we expected that the judicious choice of external ligand would be key in order to obtain a catalyst that, besides supporting the other catalytic steps (including a challenging C–H bond activation), would furthermore induce the C–O RE step and suppress the potential side reactions. Additionally, the high kinetic barrier associated with the C–O RE step would require the formation of a Pd(IV) intermediate, from which RE becomes feasible.

METHODS AND MATERIALS

Building upon the above hypotheses, we commenced our studies with 3,3-dimethyl butyric acid (**1a**) as a model substrate. Taking into consideration Yu's recent work revealing the crucial role of an N-acyl amino acid ligand and a peroxide-based oxidant in the β -lactonization reaction involving a C–O RE,^{37,38} we identified sodium percarbonate as a suitable oxidant (see Supporting Information for more details). Subsequently, guided by our recent findings,^{36,39} we performed an extensive structural investigation of β -alanine derivatives including the concerted

metalation-deprotonation (CMD)-promoting amide groups. After identifying the otherwise best reaction conditions, we re-evaluated representatives of common ligand classes (Table 1). As expected, only trace amounts of product **2a** were formed in the absence of ligand. Ligands (**L1** to **L3**) leading to a five-membered-ring chelation of the Pd catalyst delivered poor yields. As larger bite angles promote RE,⁴⁰ we turned our attention to six-membered chelating ligands. Switching to ligands with cycloalkane (**L4**), phenyl (**L5**), and linear backbone (**L6**) gave no further improvement. Prompted by our recent study³⁹ where 2,4,6-alkyl-substituted benzamide groups, in contrast to entirely inactive simple benzamides,^{41,42} were shown to be highly effective for promoting the C–H activation step, we introduced such functionalities into the β -alanine framework (**L7** and **L8**), which notably increased the yield. Considering the sometimes observed beneficial effect exerted by a methyl substituent on the ligand backbone³⁷ and our recent discovery,³⁶ where ligands combining these two design elements were shown to be effective in inducing the challenging C–F RE, a series of ligands (**L9–L11**) was tested. While **L9** continued to provide moderate yield, the catalytic efficiency improved drastically when the acetyl group in **L9** was replaced with 2,4,6-alkyl-substituted amide groups (**L10**, 67% and **L11**, 51%), presumably due to changes in the acidity of amide proton, the ligand bite angle, and increased steric hindrance favoring the challenging RE. These results highlight that the choice of CMD-promoting amide group along with the suitable placing of a substituent on the ligand backbone is crucial to enabling the desired reactivity.

Table 1. Identification of a Suitable Ligand for the γ -Lactonization^a

^aReactions were conducted on a 0.1 mmol scale. Yields were determined by ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

Having identified suitable reaction conditions, we investigated the substrate scope of our method. Due to the well-known property of alkyl-substituted γ -butyrolactones (GBLs) as potent neuropharmacologic agents,^{43,44} substantial research has been directed toward the synthesis of these scaffolds, which has typically required multiple synthetic operations.^{45,46} Using our method, GBLs **2a–2c** with different alkyl substitution at the γ -position can now be accessed in a single step with useful yields. A variety of heteroatom-containing substituents was tolerated in the γ -position such as a phenoxy group (**2d**), an ester (**2e**), and a TIPS-protected hydroxyl group (**2f**), which could serve as handles to build further molecular complexity. Arene substituents with a range of functional groups on the aryl ring and varying electronic properties were found to be compatible with our reaction conditions and delivered their respective lactones (**2g–2k**) in useful yields. Notably, these substrates (**1h–1k**) are particularly challenging, due to the presence of an equidistant activated benzylic C–H bond, the activation of which would trigger side reactions/decomposition pathways, and are not described in Yu's contemporary protocol for γ -lactonization.²⁹ Our protocol was even found to be applicable for a substrate bearing a single methyl group in competition with such reactive benzylic C–H bonds, giving **2l** in moderate yield (37%). Due to the tremendous importance of spiro-lactones in medicinal chemistry,^{47,48} our method was further applied to synthesize a series of β -spiro- γ -lactones, giving **2m** (61%), fluorine-substituted **2n** (70%), **2o** (89%), as well as heteroatom-containing spirocycles **2p** (53%), **2q** (36%), and **2r** (21%) in moderate to excellent yields. It is noteworthy that products **2m** and **2o** cannot be accessed efficiently using the alternative strategies shown in Scheme 1, since these either encounter selectivity issues between γ -1° over γ -2° positions (Path A)⁷ or selectively functionalize the γ -2° position (Path B),¹⁵ which clearly highlights the complementarity of our protocol with these approaches. We then explored different substituents at the

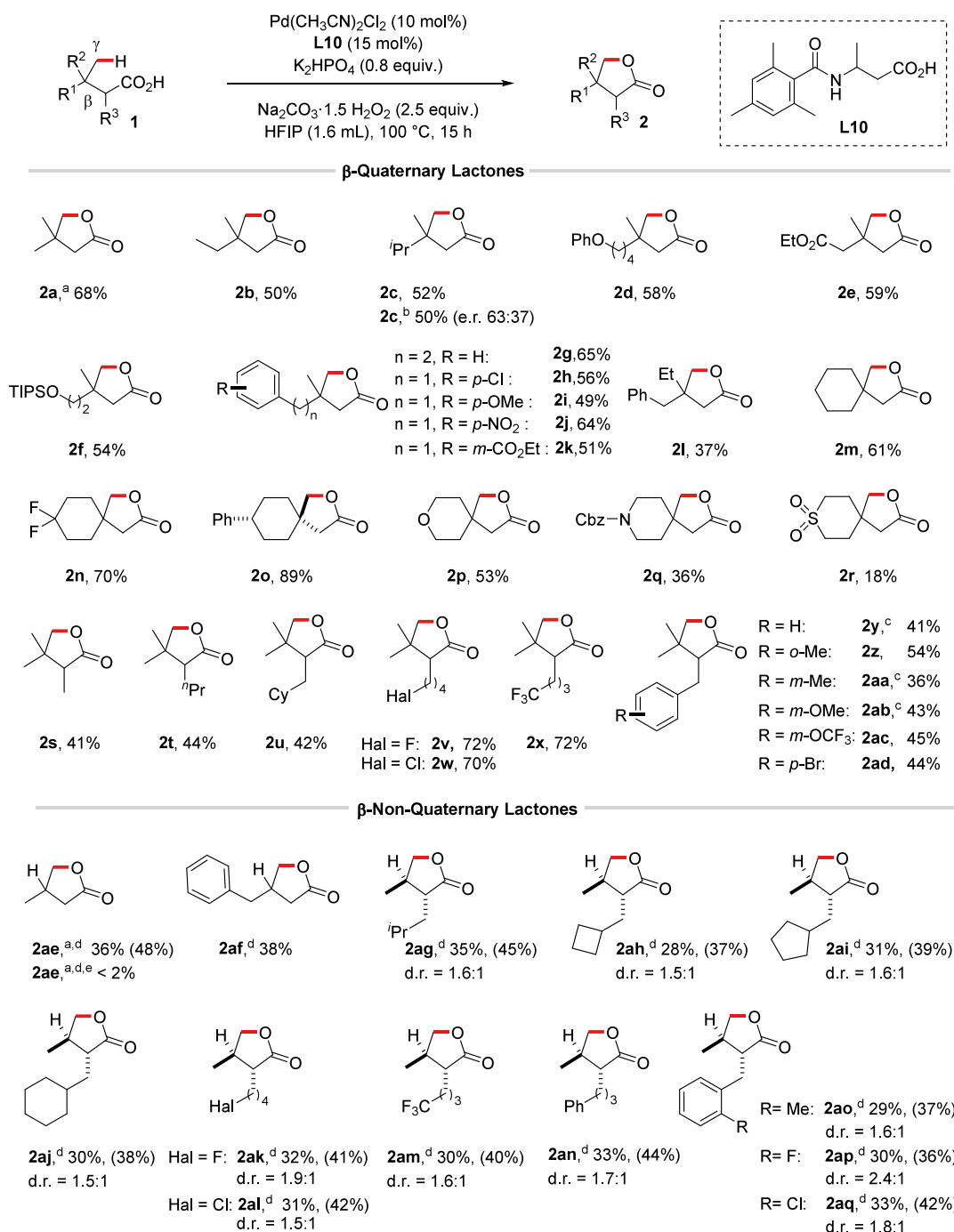
α -position. Lactones with a broad range of substituents including alkyl chains (**2s**, **2t**), a cycloalkane moiety (**2u**), halides (**2v**, **2w**), and a trifluoromethyl group (**2x**) were obtained in useful yields. Furthermore, lactones bearing electron-rich arenes (**2y–2ab**) were accessible with a slight adjustment in the reaction conditions, while electron-poor arenes such as **2ac** (45%) and **2ad** (44%) showed reasonable reactivity under standard reaction conditions. Notably, in these substrates, the γ -C–H bond activation needs to overcome a competition with decomposition pathways via activated benzylic C–H bonds in the β -position.

We then turned our attention to challenging β -non-quaternary acids, the selective functionalization of which through a palladium-catalyzed γ -C(sp³)–H activation is, to the best of our knowledge, unprecedented due to a lack of an accelerating Thorpe–Ingold effect and side reactions such as β -H-elimination.^{19,29,49–58} Gratifyingly, after a slight adjustment of the reaction conditions, the commercially available substrate 3-methyl butanoic acid afforded **2ae**, which has not been accessible in synthetically useful yield using the strategies discussed in Scheme 1,⁷ in 48% (¹H NMR) yield. A re-evaluation of ligands for β -non-quaternary substrates revealed the crucial role of ligand control in enabling this transformation (see SI for details). The fact that **L9** gave almost no product formation (Scheme 2) highlights the crucial role of the 2,4,6-alkyl-substituted CMD-promoting benzamide group in accessing β -non-quaternary acids as substrates for the first time. A substrate with a reactive benzylic position was well-tolerated (**2af**, 38%) as well as a broad range of substituents at the α -position including isopropyl (**2ag**), cycloalkane rings (**2ah–2aj**), halogens (**2ak–2al**), trifluoromethyl groups (**2am**), and phenyl groups (**2an**), showing moderate diastereoselectivities in favor of the *trans*-configured diastereomer. Furthermore, a series of lactones with α -benzyl groups (**2ao–2aq**) was successfully synthesized. While the β -non-quaternary lactones were obtained in moderate yields, the small difference between conversion and yield (see SI for more details) indicates no significant side product formation occurred.

To further probe the synthetic utility of our protocol, we first showed that it can be conducted on a preparatively useful scale. Two representative lactonizations of β -quaternary acids were performed on a 2 mmol scale giving **2m** and **2g** in 58% and 60% yield respectively (Scheme 3A), while **1ae**, a representative β -non-quaternary acid, delivered **2ae** in 34% yield (see SI for more details). Next, we investigated possible derivatizations of product **2g**. Reduction of **2g** with LiAlH₄ led to 1,4-diol **3a** (92%, Scheme 3B), a scaffold present in biologically active compounds⁵⁷ and with widespread applications, including polymer industry.⁵⁸ Considering the importance of hydroxy fatty acids in various fields,^{59,60} **2g** was subjected to hydrolysis affording **3b** (98%) in the form of a lithium salt, which can serve as precursor for further photoredox-catalyzed decarboxylative functionalization reactions.⁶¹ Finally, the aminolysis of **2g** delivered γ -hydroxy amide (**3c**, 83%), a bioactive moiety for example featuring in anticonvulsants.⁶²

Based on the literature precedence,^{26–28,37,38,49–56,63–70} our transformation is proposed to proceed via a Pd(II)/Pd(IV) catalytic cycle illustrated in Scheme 4. First, the active catalyst is generated upon the coordination of external ligand (**L10**) to Pd^{II} precatalyst. The subsequent reversible C–H activation step,^{50,53} which is accelerated by both the counteranion (Na⁺/K⁺) and the ligand, occurs via the concerted metalation–deprotonation (CMD) pathway, in which the ligand acts as an internal base to

Scheme 2. Substrate Scope of the Lactonization of Aliphatic Carboxylic Acids*



*Reactions were conducted on a 0.2 mmol scale. ¹H NMR yields reported in parentheses were determined using CH_2Br_2 as the internal standard. Whenever this could be determined from crude NMR spectra, the mass balance was found to be almost completely accounted for by product and unconverted starting material (see SI for details). ^a¹H NMR yield calculated using 1,3,5-trimethoxybenzene as the internal standard. ^b(S)-**L10** was used instead of racemic **L10**. ^c Ag_2CO_3 (1.25 equiv) was used at 90 °C for 72 h. ^d**L10** (25 mol %) and HFIP (2.5 mL) were used at 90 °C for 48 h. ^e**L9** was used as the ligand instead of **L10**.

produce **Int-1**.⁶³ Considering the well-known ability of peroxides to oxidize Pd(II) to Pd(IV),^{64–66} **Int-1** is expected to undergo an oxidative addition with hydrogen peroxide resulting in the formation of **Int-2**.^{67–69} Due to the relative ease of $\text{C}(\text{sp}^3)\text{—O}$ reductive elimination (RE) from high-valent transition-metal species,^{26,27,38,70} **Int-2** is then expected to undergo selective reductive elimination to yield the desired γ -

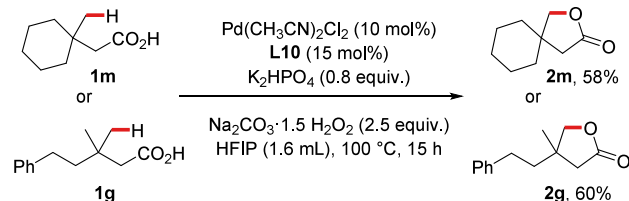
lactone (see SI for a detailed discussion) and regenerate the active catalyst via subsequent ligand exchange.

CONCLUSION

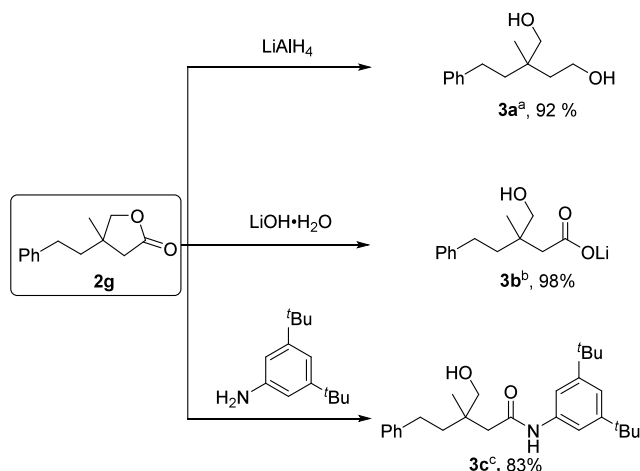
In summary, we have developed a Pd(II)-catalyzed direct γ - $\text{C}(\text{sp}^3)\text{—H}$ lactonization of aliphatic carboxylic acids based on C—O reductive elimination. The use of sodium percarbonate as an oxidant and the development of a new β -alanine-derived

Scheme 3. Synthetic Utility of the γ -Lactonization of Aliphatic Carboxylic Acids⁴

A. Scalability of the lactonization — 2.0 mmol scale

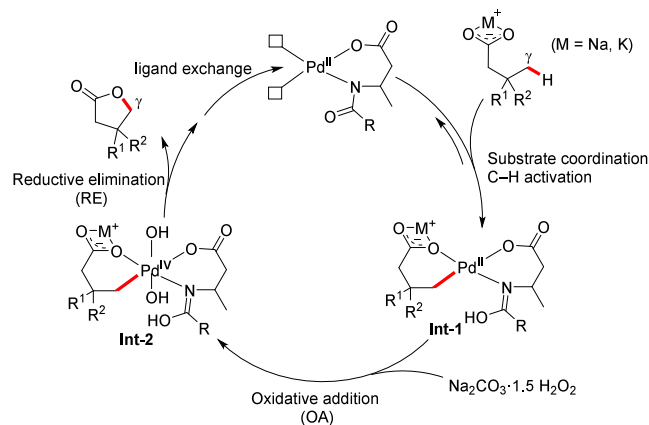


B. Derivatization of the product 2g



^a2g (0.3 mmol), LiAlH₄ (1.0 equiv), THF, rt, 12 h. ^b2g (0.2 mmol), LiOH·H₂O (1.0 equiv), THF:H₂O (1:1), 70 °C, 8 h. ^c2g (0.3 mmol), 3,5-di-*tert*-butylaniline (1.1 equiv), *n*-BuLi (2.5 M in hexanes, 2.2 equiv), −78 °C, 2 h.

Scheme 4. Proposed Catalytic Cycle of the γ -Lactonization of Aliphatic Carboxylic Acids



ligand were key to establish this protocol, which converts a wide range of carboxylic acids, for the first time including challenging β -non-quaternary acids, into the corresponding lactones in a single step. Notably, our lactonization protocol is complementary to state-of-the-art methods for the direct lactonization of free carboxylic acids and gives access to a wide library of lactones that were previously only accessible through multistep synthetic routes. Besides the synthetic utility of the protocol described herein, the discovery of a catalyst capable of functionalizing β -non-quaternary acids is expected to encourage further research

and substantially broaden the chemical space accessible through the γ -C(sp³)-H activation of aliphatic carboxylic acids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.4c08042>.

Optimization of reaction conditions, preparative procedures, and analytical data for the compounds prepared in this study (PDF)

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Author Contributions

[‡]T.X. and S.M. contributed equally. S.M. designed the ligand for lactonization. T.X. and S.M. optimized the reaction conditions and studied the scope of the transformations. M.v.G. supervised the study. The study was conceptualized through contributions by all authors. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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