Ligand-Enabled β-C(sp^3)–H Lactonization: A Stepping Stone for General and Practical β-C–H Functionalizations

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Abstract: β-C–H functionalization of aliphatic acids is emerging as a valuable synthetic disconnection that complements a wide range of conjugate addition reactions. Despite two decades of effort on β-C–H functionalizations, reported reactions bear numerous challenges, especially for industrial-scale applications due to the use of expensive oxidants and poor scope. For example, arylation reactions are only compatible with aryl iodides but not the more practical aryl bromides and chlorides, alkylations are limited to primary alkyl coupling partners; fluorination and amination reactions have not been possible using free carboxylic acids as directing groups. The unselective formation of mono- and di-functionalized products is another major drawback. Herein, we report an unprecedented palladium-catalyzed β-C(sp^3)–H lactonization of aliphatic acids enabled by a mono-*N*-protected β-amino acid ligand. The highly strained and reactive β-lactone products are versatile linchpins for the mono-selective installation of diverse alkyl, alkenyl, aryl, alkynyl, fluoro, hydroxyl, and amino groups at the β position of the parent acid, thus providing a one-for-all strategy to synthesize a myriad of carboxylic acids. The use of inexpensive *tert*-butyl hydrogen peroxide (TBHP) as the oxidant, as well as the ease of product purification without column chromatography renders this reaction amenable to ton-scale manufacturing.

Main Body:

The past two decades have witnessed rapid development of carbon-carbon (C–C) and carbon-heteroatom (C–Y) bond-forming reactions based on the palladation of C(sp^3)–H bonds[1-3]. Alkyl

carboxylic acids are ubiquitous and inexpensive reagents in organic chemistry available in a great diversity of substitution patterns – as such, they are highly desirable substrates for C–H activation reactions[4-5]. To access a wide range of β-substituted aliphatic acids, diverse transformations for the installation of different carbon fragments or functional groups must be developed. Considering the challenge of developing C–H activation reactions, it is not surprising that achieving different transformations requires independent catalyst design and directing group optimizations in each case, while the scope of these transformations is often limited due to the incompatibility of certain reaction partners. Indeed, for C–C bond formations, alkylation reactions are limited to primary alkyl iodide or alkyl boron coupling partners[6-8], olefination reactions are limited to electron-deficient olefins[9,10], alkynylation reactions are limited to silyl acetylene bromide[11], and arylation reactions are only compatible with aryl iodides but not the more practical aryl bromides and chlorides[12-15] despite the design of various directing groups. Notably, the majority of these reactions are incompatible with free aliphatic acids without exogenous directing groups. Most importantly, C–heteroatom bond-forming reactions (fluorination, hydroxylation, amination etc.) based on β-C–H activation of free aliphatic acids have not yet been realized (Figure 1A).

β-Lactones are strained heterocycles that have received significant attention as valuable synthetic intermediates in natural and unnatural products synthesis[16]. Due to their inherent ring strain, they readily react with a wide range of nucleophiles by either acyl C–O or alkyl C–O bond cleavage, in a myriad of transformations. As such, the β-lactonization of free carboxylic acids would be an ideal stepping stone to access these diverse products (Figure 1B). Moreover, the formation of the β-lactones from aliphatic acids ensures exclusive mono-selectivity and so provides an effective solution to a long-standing problem in β-C–H functionalizations. Notably, this β-lactonization could provide a one-for-all strategy to synthesize carboxylic acids containing

α-quaternary centers that are inaccessible from a conjugate addition disconnection, and difficult to prepare via α-substitution[17].

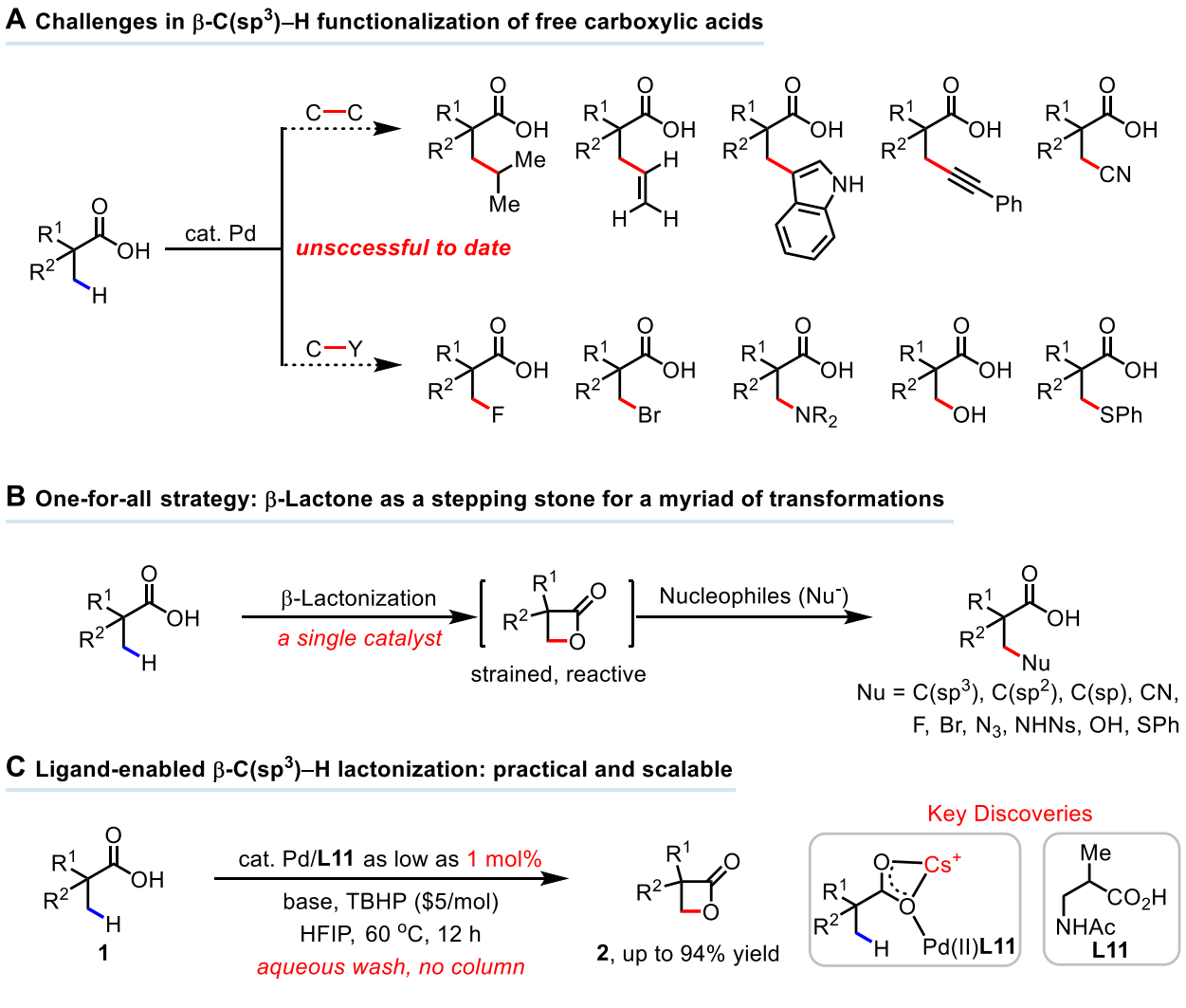

Fig. 1: **A**. Challenges in β-C(sp^3)–H functionalization of free carboxylic acids. **B**. One-for-all strategy: β-Lactone as a stepping stone for a myriad of transformations. **C**. Ligand-enabled β-C(sp^3)–H lactonization: practical and scalable.

In a pioneering example reported by Sen, a mixture of K_2PtCl_4, (17 mol%), K_2PtC1_6 (33 mol%) can promote the formation of γ-lactones from aliphatic acids in 16% yield, accompanied by 2% β-lactone[18,19]. γ-Lactonization of benzylic C–H bonds has also been reported using Pd and Pt

catalysts[20,21]. Guided by previous work using a bystanding oxidant to promote C–H activation/cyclization reactions[22,23], we began to investigate catalysts and conditions to achieve an unprecedented β-C–H lactonization reaction (Figure 1C). Compared to β-lactam formation, where a nucleophilic directing group can be employed to form a strong C–N bond[24], β-C–H lactonization is extremely challenging due to the low nucleophilicity of the carboxylic acid and the strain generated in forming a four-membered ring. We selected 2,2-dimethylbutyric acid **1a** as a model substrate when searching for reactivity with a wide range of oxidants and catalysts. Through extensive experimentation, we found that the desired β-lactone **2a** was formed in 15% NMR yield using a combination of $Pd(CH_3CN)_2Cl_2$, $CsHCO_3$ and HFIP solvent. Encouragingly, no γ-lactone or β-, γ-hydroxylated products were observed during the reaction; other Pd(II) catalysts were ineffective, suggesting the importance of the Pd-Cl bond in favoring the selective C–O reductive elimination to form a lactone. Critically, the inexpensive TBHP was identified as the most effective oxidant[4].

In light of the recent advances in ligand-accelerated Pd(II)-catalyzed C–H activation[25], we next began to search for ligands that could significantly improve the reactivity of the catalyst. Using the mono-*N*-protected α-amino acid (MPAA) ligand *N*-acetyl glycine **L1**, the yield was improved to 36%. However, extensive modification of the backbone of the α-amino acid ligand led only to minor improvements (**L2** to **L5**). Considering the challenging reductive elimination of a strained four-membered ring from Pd(IV), we reasoned that switching the ligand binding mode from five- to six-membered chelation might have significant impact. To this end, we found that using commercially available *N*-acetyl β-alanine **L6** under the same conditions improved the yield to 48%. Building on this promising finding, we then investigated the influence of substituents on the ligand's side chain. We found that various substituents at the β-position slightly reduced the

reactivity (**L7** to **L10**), suggesting that steric hindrance around the NHAc moiety was detrimental to reactivity. Meanwhile, substitution at the α-position proved beneficial (**L11** to **L13**), with methyl-substituted **L11** giving 65% yield. The isolated yield of desired β-lactone could be further improved to 73% when using TBHP in decane (see supplementary materials for more optimization).

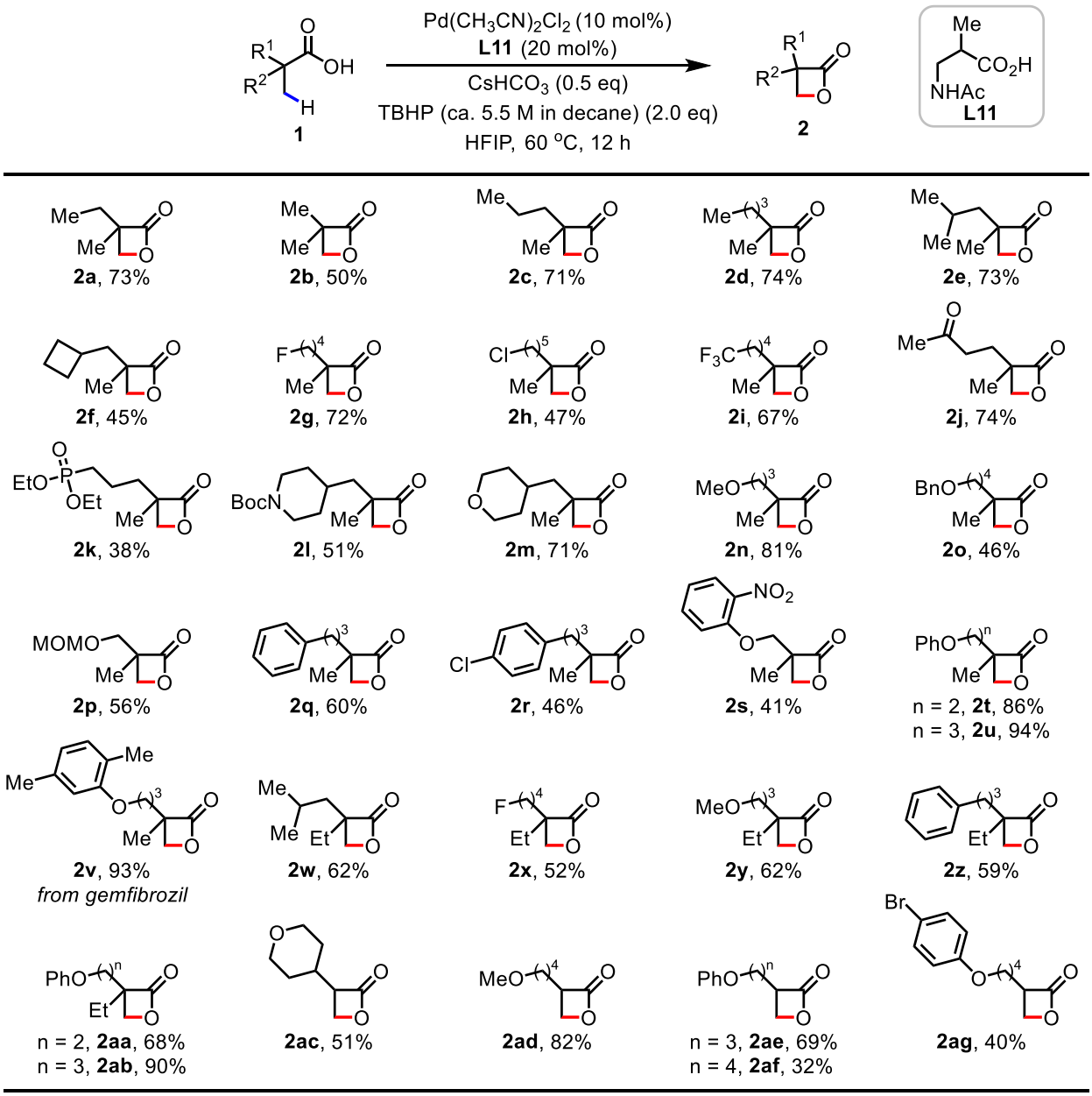

Fig. 2: Aliphatic acid scope for β-C(sp^3)–H Lactonization.

With the optimized ligand and conditions in hand, we next explored the scope of this methodology (Figure 2). Aliphatic acids containing α-gem-dimethyl groups with various aliphatic chains including cyclobutanes (**2f**) were all compatible, affording the β-lactones (**2a** to **2f**) in high yields. A range of functionalities such as fluoro (**2g**), chloro (**2h**), trifluoromethyl (**2i**), ketone (**2j**), and phosphoric ester (**2k**) were tolerated, with halogen (**2h**), ketone (**2j**) and phosphoric ester (**2k**) moieties serving as useful synthetic handles for subsequent derivatization. The lactone products containing a piperidine (**2l**) or a tetrahydropyran (**2m**) motif are especially valuable. Different protecting groups on the hydroxyl group including simple methyl (Me) (**2n**), benzyl (Bn) (**2o**), and methoxymethyl (MOM) (**2p**) were also well tolerated. Phenyl (**2q** to **2r**) and phenyl ether (**2s** to **2v**) groups were compatible with the TBHP system, and remained intact despite the potentially reactive aryl or benzylic C–H bonds. A range of substituents on the aryl ring from electron-donating (Me and O-alkyl) to electron-deficient (chloro, bromo, and nitro) groups were all well tolerated. Gemfibrozil (**1v**), an oral drug used to lower lipid levels[26], was converted to the corresponding β-lactone **2v** in high yield. This lactone could serve as a versatile intermediate for library construction in medicinal chemistry (*vide infra*). Notably, the remaining α-methyl group from the above cases could then undergo further C–H functionalizations to afford greater structural diversity. Tertiary aliphatic acids containing a single α-methyl group (**2w** to **2ab**) consistently afforded useful yields, in addition to those substrates containing α-hydrogens (**2ac** to **2ag**).

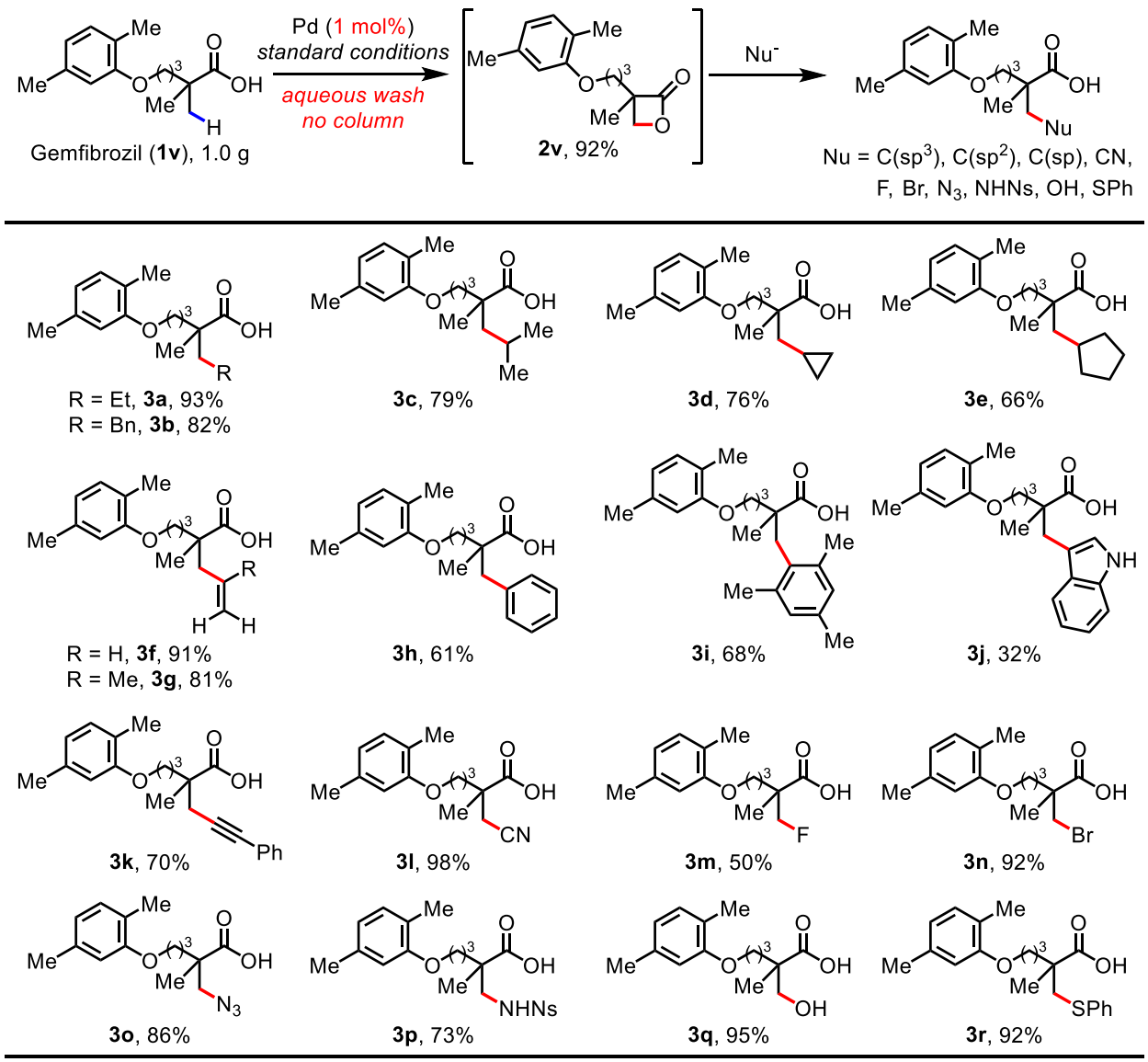

Fig. 3: Gram-scale β-C(sp^3)–H lactonization of Gemfibrozil with 1 mol% Pd and diverse transformations.

To demonstrate the scalability and practicality of this transformation, we conducted a gram-scale β-lactonization of Gemfibrozil (**1v**) with 1 mol% Pd (Figure 3). Pure product was obtained by a simple aqueous wash without chromatography. 1.0 g Gemfibrozil (**1v**) in HFIP, $Pd(OAc)_2$ (1.0 mmol%), commercially available MPAA ligand **L6** (2.0 mmol%), and NaOAc (1.0 eq) were added to a reaction tube, followed by TBHP (70% in water) (2.0 eq). After stirring at 60 °C for 24 hours, the HFIP solvent was removed by evaporation, followed by dissolution with ethyl acetate,

and washing with saturated $NaHCO_3$ solution to remove unreacted acid, ligand, and metal complex. Evaporation of solvent delivered the lactone product **2v** in 92% yield. From a practical standpoint, this reaction has several key advantages over other C–H activation protocols: (1) the inexpensive oxidant TBHP is used; (2) the reaction tolerates air and moisture; (3) the reaction may be reliably scaled-up; (4) a simple aqueous wash delivers the final product without chromatography.

As depicted in Figure 3, β-lactone product **2v** is a stepping stone for mono-selective installation of a range of alkyl, alkenyl, aryl, alkynyl, cyano, halogen, amino, hydroxyl, and thiophenyl groups[27-29]. Various alkyl (**3a** to **3e**), alkenyl (**3f** to **3g**), and aryl (**3h** to **3j**) Grignard reagents in the presence of catalytic copper were able to successfully open the β-lactone to build new C–C bonds at the β-position of the parent aliphatic acids[25,26]. In particular, secondary alkyl structure motifs such as isopropyl (**3c**), cyclopropyl (**3d**), and cyclopentyl (**3e**) could be efficiently installed; in contrast, the analogous secondary alkyl iodides are usually incompatible in Pd-catalyzed C–H alkylation reactions. β-Vinyl aliphatic acids (**3f** to **3g**) were directly accessible through reaction with their corresponding vinyl (**3f**) and isopropenyl (**3g**) Grignard reagents, which provided a strategy complementary to the Pd catalyzed β-C–H olefination of free acids and their derivatives, where only electron-deficient olefins were effective. β-Lactone **2v** may also be expediently elaborated into corresponding β-arylated aliphatic acids (**3h** to **3j**); this approach is particularly strategic in the case of **3i** and **3j**, as the corresponding iodides are often not a viable coupling partner. The use of Grignard reagents prepared from readily available aryl bromides or chlorides is also a practical advantage. Additionally, β-phenylacetylene aliphatic acids **3k** could be successfully synthesized from β-lactone **2v** on treatment with alkynyl aluminum reagent. Cyanide could also open the lactone to construct a new C–C bond, affording the corresponding β-cyano

aliphatic acids (**3l**). The electrophilicity of the β-lactone carbonyl was further exploited by the addition of the weak fluoride nucleophile (**3m**) to introduce a CH_2F fragment, a highly sought-after bioisostere in medicinal chemistry. By a similar β-lactone opening, $MgBr_2$ delivered the formally β-brominated aliphatic acid (**3n**) in high yield, a versatile linchpin for further elaboration. Further manipulations of the β-lactone in the presence of hard nucleophiles NaN_3 or NaNHNs afforded coveted β-amino acid scaffolds (**3o** to **3p**) in consistently high yields. By making use of the β-lactone as a masked aldol adduct, mild hydrolysis afforded the β-hydroxyl acid **3q** in high yield. Finally, the formal β-chalcogenation product **3r** was obtained in near quantitative yield using thiophenol sodium salt as a nucleophile.

In summary, we have realized an effective β-lactonization of ubiquitous aliphatic acids enabled by a single Pd(II) catalyst bearing a mono-*N*-protected β-amino acid ligand. The diverse reactivity of the resultant β-lactones establishes an one-for-all disconnection for diverse β-functionalized aliphatic acids with exclusive mono-selectivity and unparalleled scope. The use of inexpensive TBHP as the sole oxidant and purification by a simple aqueous work-up without chromatography render this reaction highly practical and potentially amenable for ton-scale manufacturing.

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Author Contributions: J.-Q. Y. conceived the concept. Z. Z. developed the lactonization reaction. J.-Q. Y. directed the project.

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