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Lactonization as a general route to β-C(sp³)–H functionalization

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Summary Paragraph

Functionalization of the β-C–H of aliphatic acids is emerging as a valuable synthetic disconnection that complements a wide range of conjugate addition reactions[1–5]. Despite efforts on β-C–H functionalizations for carbon-carbon (C-C) and carbon-heteroatom (C-Y) bond-forming reactions, these bear numerous decisive limitations, especially for industrial-scale applications, including the lack of mono-selectivity, use of expensive oxidants, and limited scope[6–13]. Notably, the majority of these reactions are incompatible with free aliphatic acids without exogenous directing groups. 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. Here, we report a Pd-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 route to myriad carboxylic acids. The use of inexpensive *tert*-butyl hydrogen peroxide (TBHP) as the oxidant to promote the desired selective reductive elimination from the Pd(IV) center, as well as the ease of product purification without column chromatography renders this reaction amenable to ton-scale manufacturing.

Main Text

Alkyl carboxylic acids are ubiquitous and inexpensive reagents in organic chemistry – as such, they are privileged substrates for C–H activation reactions[4,5]. 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[12,13] despite the design of various 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. Considering these persistent limitations of the conventional β-C–H activation approach, we turned to a one-for-

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all β-lactonization strategy (Fig. 1a). β-Lactones are strained heterocycles that have received significant attention as valuable synthetic intermediates in natural and unnatural products synthesis[14,15]. 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. The lack of precedent of this reaction is likely due to the highly unfavored four-membered lactonization transition state[15]. Notably, this β-lactonization could provide a strategy to synthesize carboxylic acids containing α-quaternary centers that are inaccessible by conjugate addition chemistry, and difficult to prepare via α-substitution[16].

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[17,18]. γ-Lactonization of benzylic C–H bonds has also been reported using Pd and Pt catalysts[19,20]. These observations indicate that β-lactonization is a highly disfavored process. Guided by previous work using a bystanding oxidant to promote C–H activation/cyclization reactions[21,22], we began to investigate catalysts and conditions to achieve an unprecedented β-C–H lactonization reaction. Compared to β-lactam formation, where a nucleophilic directing group can be employed to form a strong C–N bond[23,24], β-C–H lactonization poses an additional challenge due to the low nucleophilicity of the carboxylic acid, the strain generated in forming a four-membered ring, and the facile ring opening under C–H activation conditions. Most problematically, Pd(IV) intermediates could readily undergo conventionally favored reductive elimination to form non-cyclic C–O bond formation products such as the most common competing pathways acetoxylation and alkoxylation (Fig. 1b). We selected 2,2-dimethylbutyric acid **1a** as a model substrate when searching for reactivity with a wide range of oxidants and catalysts. The exploratory studies using various common oxidants for Pd(II)/Pd(IV) chemistry, such as $PhI(OAc)_2$, $K_2S_2O_8$, and F^+ reagents, consistently gave the undesired non-cyclic oxidation products (see Supplementary Information Table S3 and Mechanistic Studies section for details). To avoid the undesired reductive elimination pathway, we tested the sterically bulky oxidant TBHP[4] as well as the $PdCl_2$ derived catalysts as the ^{t}BuO and Cl anion is less prone to reductive elimination due to sterics and electronics. The desired β-lactone **2a** was formed in 15% NMR yield using a combination of $Pd(CH_3CN)_2Cl_2$, TBHP oxidant, $CsHCO_3$ and HFIP solvent. Encouragingly, no γ-lactone or β-, γ-hydroxylated products were observed during the reaction. The unique role of TBHP for favoring β-lactone formation can be rationalized based on the studies on the oxidation of Pd(II) to Pd(IV) by benzoyl peroxide[25] and TBHP[4]. Following the oxidation of Pd(II) to Pd(IV) by TBHP, ^{t}BuO$^-$ and HO$^-$ bound to Pd(IV) center are less likely to undergo rapid reductive elimination due to the strong Pd–O^{t}Bu (OH) bond. Based on the principle of organometallic chemistry, the steric hindrance of ^{t}BuO$^-$ could also enhance the reductive elimination of the carboxylate from substrate to generate β-lactone product.

In light of the recent advances in ligand-accelerated Pd(II)-catalyzed C–H activation[26], we next began to search for ligands that could significantly improve the reactivity of the catalyst. It is also possible an appropriate ligand could enhance the otherwise unfavored β-lactonization. Using the mono-*N*-protected α-amino acid (MPAA) ligand *N*-acetyl glycine **L1**, the yield was improved to 36%. 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 will increase the bite angle thereby favoring the desired reductive elimination. The β-amino acid-derived ligand *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. 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 β-lactone could be further improved to 73% when using TBHP in decane (see Supplementary Information for more optimization).

With the optimized ligand and conditions in hand, we next explored the scope of this methodology (Fig. 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[27], 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**).

To demonstrate the scalability and practicality of this transformation, we conducted a gram-scale β-lactonization of Gemfibrozil (**1v**) with 1 mol% Pd (Fig. 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; (2) tolerant of air and moisture; (3) reliably scale-up; (4) aqueous wash delivers the product without chromatography.

As depicted in Fig. 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[28–30]. 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[28,29]. 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.

Methods

General Procedure for β-C(sp^3)–H Lactonization

In the culture tube, $Pd(CH_3CN)_2Cl_2$ (10 mol%, 2.6 mg), ligand **L11** (20 mol%, 2.9 mg), $CsHCO_3$ (0.5 eq, 9.7 mg), and carboxylic acid **1** (0.1 mmol) in order were weighed in air and placed with a magnetic stir bar. Then HFIP (1.0 mL) and TBHP (ca. 5.5 M in decane) (2.0 eq, 36 μL) were added. The reaction mixture was stirred at rt for 3 min, and then heated to 60 °C for 12 hours (600 rpm). After being allowed to cool to room temperature, the mixture was concentrated *in vacuo*, and the resulting mixture was purified by preparative thin-layer chromatography or diluted with EA and washed with saturated $NaHCO_3$ solution. Full experimental details and characterization of new compounds can be found in the Supplementary Information.

Data availability

The data supporting the findings of this study are available within the article and its Supplementary Information Files.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Daugulis O, Roane J & Tran LD Bidentate, monoanionic auxiliary-directed functionalization of carbon–hydrogen bonds. Acc. Chem. Res 48, 1053–1064 (2015). [PubMed: 25756616]
2. Lyons TW & Sanford MS Palladium-catalyzed ligand-directed C–H functionalization reactions. Chem. Rev 110, 1147–1169 (2010). [PubMed: 20078038]
3. He J, Wasa M, Chan KSL, Shao Q & Yu J-Q Palladium-catalyzed transformations of alkyl C–H Bonds. Chem. Rev 117, 8754–8786 (2017). [PubMed: 28697604]
4. Giri R, Liang J, Lei J-G, Li J-J, Wang D-H, Chen X, Naggar IC, Guo Foxman, C. B. M & Yu J-Q. Pd-catalyzed stereoselective oxidation of methyl groups by inexpensive oxidants under mild conditions: a dual role for carboxylic anhydrides in catalytic C–H bond oxidation. Angew. Chem. Int. Ed 44, 7420–7424 (2005).
5. Giri R, Maugel N, Li J-J, Wang D-H, Breazzano SP, Saunders LB & Yu J-Q Palladium-catalyzed methylation and arylation of sp^2 and sp^3 C–H bonds in simple carboxylic acids. J. Am. Chem. Soc 129, 3510–3511 (2007). [PubMed: 17335217]
6. Wang D-H, Wasa M, Giri R & Yu J-Q Pd(II)-catalyzed cross-coupling of sp^3 C–H bonds with sp^2 and sp^3 boronic acids using air as the oxidant. J. Am. Chem. Soc 130, 7190–7191 (2008). [PubMed: 18479089]
7. Shabashov D & Daugulis O Auxiliary-assisted palladium-catalyzed arylation and alkylation of sp^2 and sp^3 carbon–hydrogen bonds. J. Am. Chem. Soc 132, 3965–3972 (2010). [PubMed: 20175511]
8. Zhang S-Y, Li Q, He G, Nack WA & Chen G Stereoselective synthesis of β−alkylated α−amino acids via palladium-catalyzed alkylation of unactivated methylene C(sp3)–H bonds with primary alkyl halides. J. Am. Chem. Soc 135, 12135–12141 (2013). [PubMed: 23919290]
9. Zhuang Z, Yu C-B, Chen G, Wu Q-F, Hsiao Y, Joe CL, Qiao JX, Poss MA & Yu J-Q Ligand-enabled β-C(sp3)–H olefination of free carboxylic acids. J. Am. Chem. Soc 140, 10363–10367 (2018). [PubMed: 30029574]
10. Wasa M, Engle KM & Yu J-Q Pd(II)-catalyzed olefination of sp^3 C–H bonds. J. Am. Chem. Soc 132, 3680–3681 (2010). [PubMed: 20187642]
11. Ano Y, Tobisu M & Chatani N Palladium-catalyzed direct ethynylation of C(sp3)–H bonds in aliphatic carboxylic acid derivatives. J. Am. Chem. Soc 133, 12984–12986 (2011). [PubMed: 21790123]
12. Zaitsev VG, Shabashov D & Daugulis O Highly regioselective arylation of sp^3 C–H bonds catalyzed by palladium acetate. J. Am. Chem. Soc 127, 13154–13155 (2005). [PubMed: 16173737]
13. Shen P-X, Hu L, Shao Q, Hong K & Yu J-Q Pd(II)-catalyzed enantioselective C(sp3)–H arylation of free carboxylic acids. J. Am. Chem. Soc 140, 6545–6549 (2018). [PubMed: 29741883]
14. Wang Y, Tennyson RL & Romo D β-Lactones as intermediates for natural product total synthesis and new transformations. Heterocycles 64, 605–658 (2004).
15. Robinson SL, Christenson JK & Wackett LP Biosynthesis and chemical diversity of β-lactone natural products, Nat. Prod. Rep 36, 458–475 (2019). [PubMed: 30191940]
16. Quasdorf KW & Overman LE Catalytic enantioselective synthesis of quaternary carbon stereocentres. Nature 516, 181–191 (2014). [PubMed: 25503231]
17. Kao L-C & Sen A Platinum(II) catalysed selective remote oxidation of unactivated C–H bonds in aliphatic carboxylic acids. J. Chem. Soc., Chem. Commun 1242–1243 (1991).

18. Dangel BD, Johnson JA & Sames D Selective functionalization of amino acids in water: a synthetic method via catalytic C–H bond activation. J. Am. Chem. Soc 123, 8149–8150 (2001). [PubMed: 11506585]
19. Lee JM & Chang S Pt-Catalyzed sp^3 C–H bond activation of *o*-alkyl substituted aromatic carboxylic acid derivatives for the formation of aryl lactones. Tetrahedron Lett. 47, 1375–1379 (2006).
20. Novák P, Correa A, Gallardo-Donaire J & Martin R Synergistic palladium-catalyzed C(sp3)–H activation/C(sp3)–O bond formation: a direct, step-economical route to benzolactones. Angew. Chem. Int. Ed 50, 12236–12239 (2011).
21. Mei T-S, Wang X & Yu J-Q Pd(II)-catalyzed amination of C–H bonds using single-electron or two-electron oxidants. J. Am. Chem. Soc 131, 10806–10807 (2009). [PubMed: 19606861]
22. Engle KM, Mei T-S, Wang X & Yu J-Q Bystanding F^+ oxidants enable selective reductive elimination from high-valent metal centers in catalysis. Angew. Chem. Int. Ed 50, 1478–1491 (2011).
23. Zhang Q, Chen K, Rao W, Zhang Y, Chen F-J & Shi B-F Stereoselective synthesis of chiral α-amino-β-lactams through palladium(II)-catalyzed sequential monoarylation/amidation of C(sp3)–H bonds. Angew. Chem. Int. Ed 52, 13588–13592 (2013).
24. McNally A, Haffemayer B, Collins BSL & Gaunt MJ Palladium-catalysed C–H activation of aliphatic amines to give strained nitrogen heterocycles. Nature 510, 129–133 (2014). [PubMed: 24870240]
25. Canty AJ, Jin H, Skelton BW & White AH Oxidation of complexes by (O2CPh)2 and (ER)2 (E = S, Se), including structures of Pd(CH2CH2CH2CH2)(SePh)2(bpy) (bpy = 2,2'-Bipyridine) and MMe2(SePh)2(L2) (M = Pd, Pt; L2 = bpy, 1,10-phenanthroline) and C···O and C···E bond formation at palladium(IV). Inorg. Chem 37, 3975–3981 (1998). [PubMed: 11670512]
26. Wang D-H, Engle KM, Shi B-F & Yu J-Q Ligand-enabled reactivity and selectivity in a synthetically versatile aryl C–H olefination. Science 327, 315–319 (2010). [PubMed: 19965380]
27. Todd PA & Ward A Gemfibrozil - a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in dyslipidaemia. Drugs 36, 314–339 (1988). [PubMed: 3056692]
28. Sato T, Kawara T, Kawashima M & Fujisawa T Copper-catalyzed reaction of Grignard reagents with β-propiolactones: a convenient method for the synthesis of β-substituted propionic acids. Chem. Lett 9, 571–574 (1980).
29. Smith ND, Wohlrab AM & Goodman M Enantiocontrolled synthesis of α-methyl amino acids via Bn2N-α-methylserine-β-lactone. Org. Lett 7, 255–258 (2005). [PubMed: 15646971]
30. Arnold LD, Kalantar TH & Vederas JC Conversion of serine to stereochemically pure β-substituted α-amino acids via β-Lactones. J. Am. Chem. Soc 107, 7105–7109 (1985).

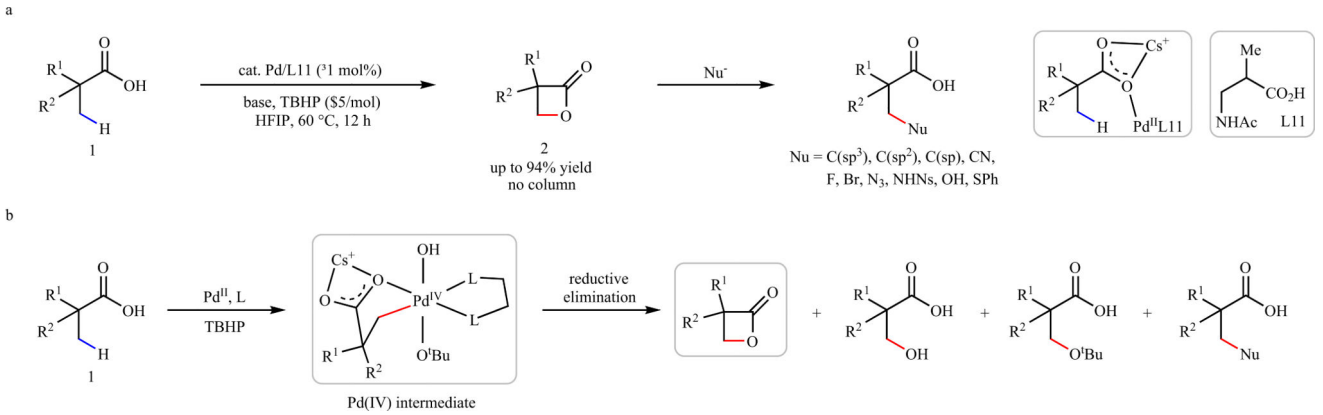

Fig. 1. β-C(sp^3)–H functionalization.

a, Lactonization as a general and scalable route to β-C(sp^3)–H functionalization. **b**, Challenges: multiple reductive elimination pathways of Pd^{IV} centers (Nu = nucleophile = acid, solvent, etc). L = ligand, TBHP = *tert*-butyl hydroperoxide, HFIP = 1,1,1,3,3,3-Hexafluoro-2-propanol.

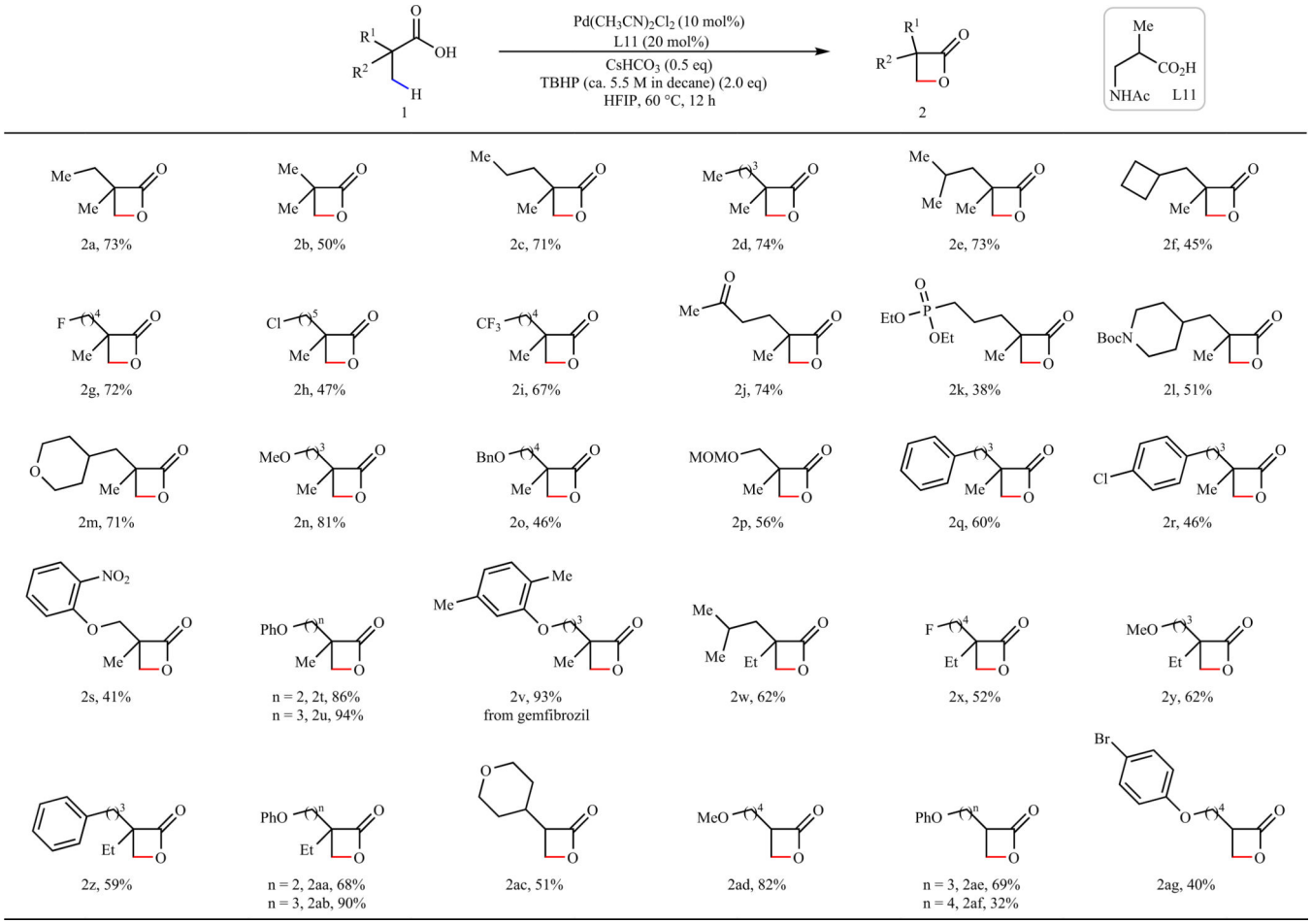

Fig. 2. Aliphatic acid scope for β-C(sp^3)–H lactonization.
See Supplementary Information for details.

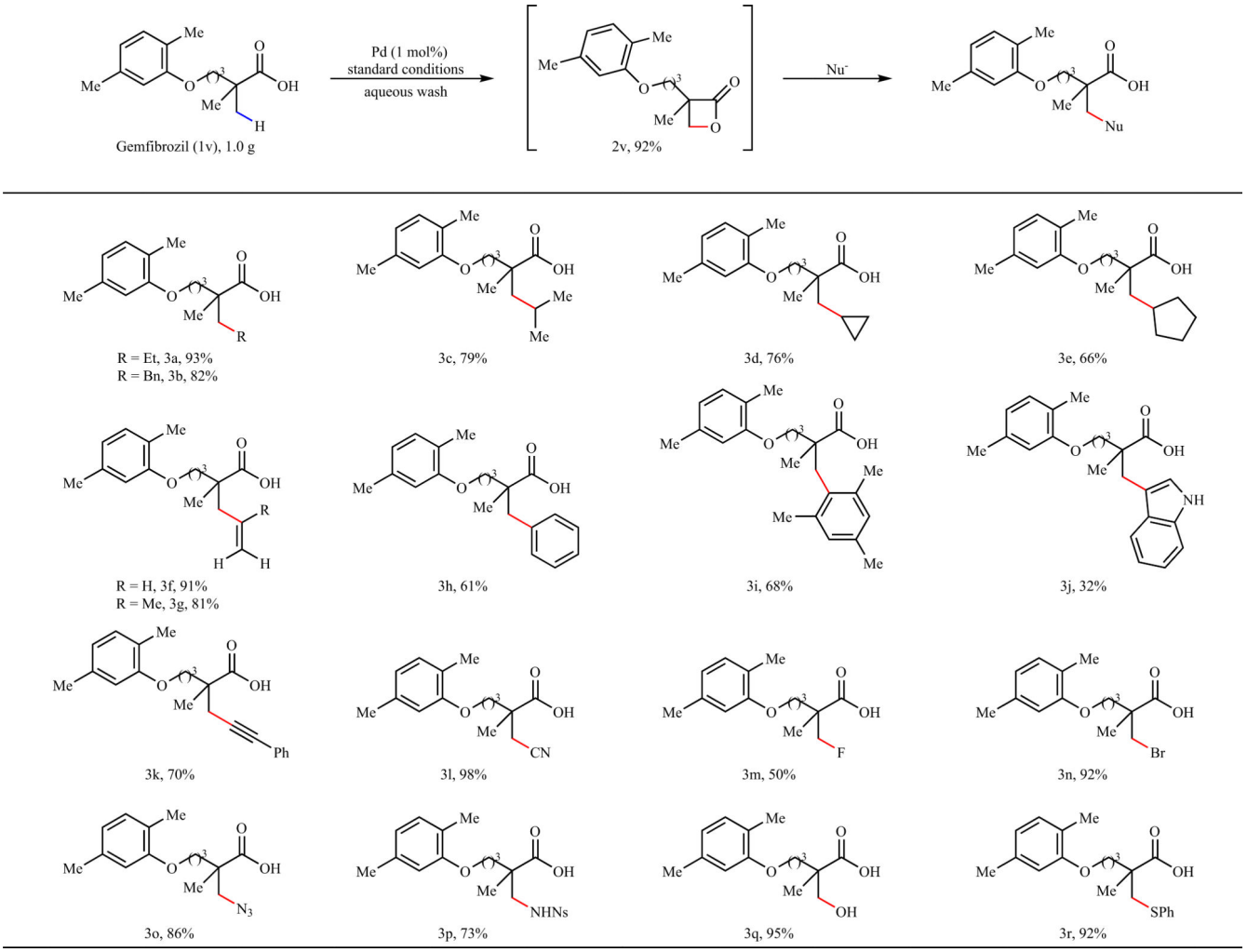

Fig. 3. Gram-scale β-C(sp^3)–H lactonization of Gemfibrozil with 1 mol% Pd and diverse transformations.

Nu = Grignard reagents (**3a** to **3j**), alkynylaluminum reagent (**3k**), TBACN (**3l**), TBAF (**3m**), $MgBr_2$ (**3n**), NaN_3 (**3o**), NaNHNs (**3p**), KOH (**3q**), PhSNa (**3r**). See Supplementary Information for details.