Alkyl carboxylic acids are ubiquitous and inexpensive reagents in organic chemistry; as such, they are favourable substrates for C–H activation reactions. The scope of such transformations is often limited by 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; olefination reactions are applicable only to electron-deficient olefins; alkynylation reactions are limited to silyl acetylene bromide; and arylation reactions are compatible only with aryliodides, but not with the more practical aryl bromides and chlorides, despite the design of various directing groups. Most importantly, carbon–heteroatom (C–Y) bond-forming reactions (such as fluorination, hydroxylation and amination) 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-all β-lactonization strategy. β-Lactones are strained heterocycles that have received considerable attention as valuable synthetic intermediates in the synthesis of natural and unnatural products. Owing 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 probably due to the highly unfavoured four-membered lactonization transition state. Notably, this β-lactonization could provide a strategy to synthesize carboxylic acids containing α-quaternary centres that are inaccessible by conjugate addition chemistry, and difficult to prepare via α-substitution.

A mixture of K2PtCl4 (17 mol%) and K2PtCl6 (33 mol%) can promote the formation of γ-lactones from aliphatic acids in 16% yield, accompanied by 2% β-lactone. γ-Lactonization of benzylic C–H bonds has also been reported using Pd and Pt catalysts. These observations indicate that β-lactonization is a highly disfavoured process. Guided by previous work using a bystanding oxidant to promote C–H activation/cyclization reactions, we investigated catalysts and conditions to achieve a 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, β-C–H lactonization poses an additional challenge because of 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 favoured reductive elimination to produce 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 as a model substrate in our search for reactivity with a wide range of oxidants and catalysts. Exploratory studies using various common oxidants for Pd(II)/Pd(IV) chemistry—such as PhIOAc, K2S2O8 and F− reagents—consistently gave undesired non-cyclic oxidation products (see Supplementary Information Table 3 and section ‘Mechanistic studies’ for details).

To avoid the undesired reductive-elimination pathway, we tested the sterically bulky oxidant tert-butyl hydrogen peroxide (TBHP), as well as PdCl2-derived catalysts, because the β-t-BuO and Cl anions are less prone to reductive elimination due to sterics and electronics. The desired β-lactone was formed in 15% HNMR (nuclear magnetic resonance) yield using a combination of Pd(CH3CN)2Cl2, TBHP oxidant, CsHCO3 and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) solvent. Encouragingly,
no γ-lactone or β-, γ-hydroxylated products were observed during the reaction. The unique role of TBHP in favouring β-lactone formation can be rationalized on the basis of studies on the oxidation of Pd(II) to Pd(IV) by benzoyl peroxide25 and TBHP. Following the oxidation of Pd(II) to Pd(IV) by TBHP, 'BuO− and HO− bound to a Pd(IV) centre are less likely to undergo rapid reductive elimination due to the strong Pd−O(=Bu) (OH) bond. According to the principle of organometallic chemistry, the steric hindrance of BuO− could also enhance the reductive elimination of the carboxylate from the substrate to generate β-lactone product.

In light of the recent advances in ligand-accelerated Pd(II)-catalysed C–H activation26, we next searched for ligands that could substantially improve the reactivity of the catalyst. It is also possible that an appropriate ligand could enhance the otherwise unfavoured β-lactonization. Using the mono-N-protected α-amino acid (MPAA) ligand 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

Fig. 1 | β-C(sp³)–H functionalization. a, Lactonization as a general and scalable route to β-C(sp³)–H functionalization. b, Challenges: multiple reductive-elimination pathways of Pd(IV) centres. Nu, nucleophile (acid, solvent); L, ligand.

Fig. 2 | Aliphatic acid scope for β-C(sp³)–H lactonization. Conditions for 2a to 2s and 2w to 2z: 1 (0.1 mmol), Pd(CH₃CN)₂Cl₂ (10 mol%), L11 (20 mol%), CsHCO₃ (0.5 equiv.), TBHP (~5.5 M in decane) (2.0 equiv.), HFIP, 60 °C, 12 h. Conditions for 2t to 2v and 2aa to 2ag: 1 (0.1 mmol), Pd(OAc)₂ (10 mol%), L11 (20 mol%), NaOAc (1.0 equiv.), TBHP (about 5.5 M in decane) (2.0 equiv.).
Fig. 3 | Gram-scale β-C(sp²)–H lactonization of Gemfibrozil with 1 mol% Pd and diverse transformations. Nu, Grignard reagents (3a to 3j), alkynylaluminum reagent (3k), TBACN (3l), TBAF (3m), MgBr₂ (3n), NaN₃ (3o), NaHₓN₃ (3p), KOH (3q), PhSNa (3r). Conditions for 3a to 3j: 2v (0.1 mmol).

binding mode from five- to six-membered chelation will increase the bite angle, thereby favouring the desired reductive elimination. The β-amino acid-derived ligand N'-acetylβ-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 NH₄ moiety was detrimental to reactivity. Moreover, 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 details).

After determining the optimized ligand and conditions, we 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-withdrawing (chloro, bromo and nitro) groups were all well tolerated. Gemfibrozil (Iv), an oral drug used to lower lipid levels⁴, 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 (see below). 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 (IV) with 1 mol% Pd (Fig. 3). Pure product was obtained by a simple aqueous wash without chromatography. 1.0 g gemfibrozil (IV) in HFIP, Pd(OAc)₂ (1.0 mol%), commercially available MPAA ligand L6 (2.0 mol%) and NaOAc (1.0 equiv.) were added to a reaction tube, followed by TBHP (70% in water) (2.0 equiv.). After stirring at 60 °C for 24 h, the HFIP solvent was removed by evaporation, followed by dissolution with ethyl acetate and washing with saturated NaHCO₃ solution to remove...
unreacted acid, ligand and metal complex. Evaporation of solvent delivered the lactone product **2** in 92% yield. From a practical standpoint, this reaction has several key advantages over other C–H activation protocols: (1) the inexpensive oxidant TBHP (US$5 per mole); (2) it tolerates air and moisture; (3) it can be reliably scaled up; (4) the aqueous wash delivers the product without chromatography.

As depicted in Fig. 3, the β-lactone product **2** is a stepping stone for mono-selective installation of a range of alkyl, alkenyl, aryl, alkynyl, cyano, halogen, amino, hydroxyl and thiophenyl groups. 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. In particular, secondary alkyll structure motifs, such as isopropyl (**3e**), cyclopropyl (**3d**) and cyclopentyl (**3e**), could be efficiently installed; by contrast, the analogous secondary alkyll iodides are usually incompatible in Pd-catalysed 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-catalysed β-C–H olefination of free acids and their derivatives, where only electron-deficient olefins were effective. β-Lactone **2** may also be expediently elaborated into the corresponding β-arylated aliphatic acids (**3k to 3l**); this approach is particularly crucial in the case of **3l** and **3j**, because the corresponding iodides are often not viable coupling partners. The use of Grignard reagents prepared from readily available aryl bromides or chlorides also provides a practical advantage. Additionally, β-phenylacetylene aliphatic acids **3k** could be successfully synthesized from β-lactone **2** on treatment with alkylvinyl aluminum reagent. Cyanide could also open the lactone to construct a new C–C bond, allowing the corresponding β-cyano aliphatic acids **3l**. The electrophilicity of the β-lactone carbonyl was further exploited by the addition of the weak fluorine nucleophile (**3m**) to introduce a CH2F fragment, a highly sought-after bioisostere in medicinal chemistry. By a similar β-lactone opening, MgBr2 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 the hard nucleophiles NaN3 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 aldox adduct, mild hydrolysis afforded the β-hydroxyl acid **3q** in high yield. Finally, the formal β-chalcogeneration product **3r** was obtained in near-quantitative yield using thiophenol sodium salt as a nucleophile.

**Online content**

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-019-1859-y.
Methods

General procedure for β-C(sp³)–H lactonization

Pd(CH₃CN)₂Cl₂ (10 mol%, 2.6 mg), ligand L₁₁ (20 mol%, 2.9 mg), CsHCO₃ (0.5 equiv., 9.7 mg) and carboxylic acid 1 (0.1 mmol), in that order, were weighed in air and placed in a culture tube with a magnetic stir bar. Then HFIP (1.0 mL) and TBHP (about 5.5 M in decane) (2.0 equiv., 36 μL) were added. The reaction mixture was stirred at room temperature for 3 min and then heated to 60 °C for 12 h (600 rpm). After cooling to room temperature, the mixture was concentrated in vacuo, and the resulting mixture was purified by preparative thin-layer chromatography or diluted with ethyl acetate and washed with saturated NaHCO₃ solution. The full experimental details and characterization of the new compounds can be found in Supplementary Information.

Data availability

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

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Author contributions

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

Competing interests

The authors declare no competing interests.

Additional information

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