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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.0c01214 • Publication Date (Web): 22 Mar 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Ligand-Enabled mono-Selective β-C(sp^3)–H Acyloxylation of Free Carboxylic Acids Using a Practical Oxidant

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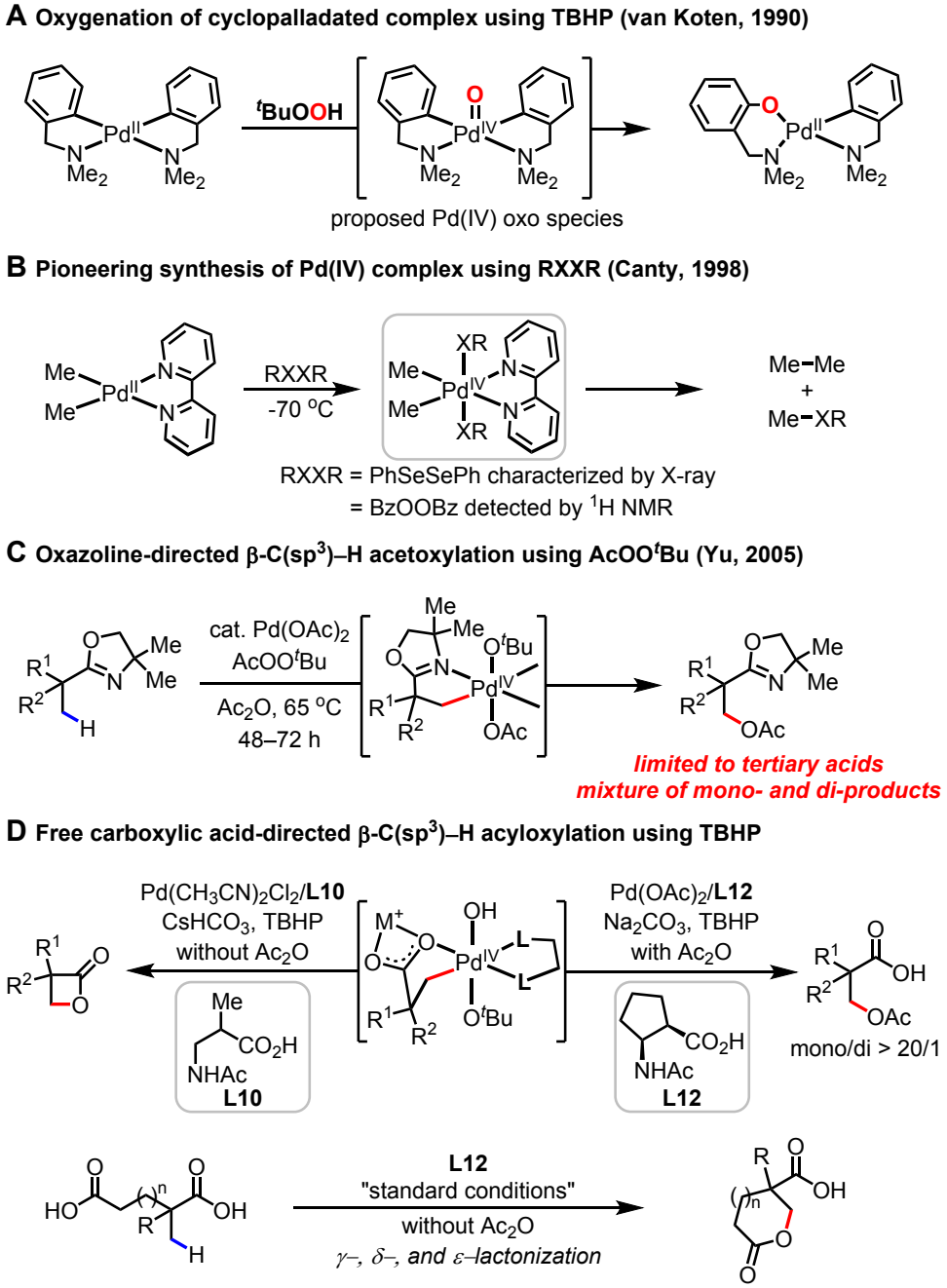
Abstract. The development of C–H activation reactions that use inexpensive and practical oxidants remains a significant challenge. Until our recent disclosure of the β-lactonization of free aliphatic acids, the use of peroxides in C–H activation reactions directed by weakly coordinating native functional groups was unreported. Herein we report C(sp^3)–H β-acetoxylation and γ-, δ-, and ε-lactonization reactions of free carboxylic acids enabled by a novel cyclopentane-based mono-*N*-protected β-amino acid (MPAA) ligand. Notably, *tert*-butyl hydrogen peroxide (TBHP) is used as the sole oxidant for these reactions. This reaction has several key advantages over other C–H activation protocols: (1) exclusive mono-selectivity was observed in the presence of two α-methyl groups; (2) aliphatic carboxylic acids containing α-hydrogens are compatible with this protocol; (3) lactonization of free acids, affording γ-, δ-, or ε-lactones, has been achieved for the first time.

1. Introduction

The past two decades have witnessed significant advances in the development of carbon–carbon and carbon–heteroatom bond-forming C–H activation reactions based on Pd(0)/Pd(II), Pd(II)/Pd(IV), Pd(II)/Pd(0), and Pd(II)/Pd(II) catalysis.[1] From a practical perspective, each catalytic cycle has inherent advantages and limitations. For example, Pd(II)/Pd(0) catalysis enables transformations with a wide range of coupling partners, such as organotin[2a] and organoboron[2b,c] reagents. Meanwhile in Pd(II)/Pd(IV) catalysis, the relatively facile reductive elimination from Pd(IV) allows the reaction of C–H bonds with a variety of electrophiles such as I_2, Cl_2, IOAc, PhSSPh, PhSeSePh, and BzOOBz.[3] Interestingly, $PhI(OAc)_2$ has been shown to be an effective oxidant for both C(sp^2)–H[4a,b] and C(sp^3)–H[4c] activation reactions. Among a range of strong oxidants that are capable of oxidizing Pd(II) to Pd(IV), inexpensive, practical, and readily available group 16 oxidants such as peroxides have received special attention. In 1990, van Koten's group reported that cyclopalladated *N*,*N*-dimethylbenzylamine complexes could be oxygenated with *tert*-butyl hydrogen peroxide (TBHP).[5] An unstable Pd(IV) oxo intermediate was proposed to give oxygenated product by oxygen insertion into the Pd–C bond. Pioneering work from Canty's group in 1998 showed that the stable Pd(IV) complex from the oxidation of Pd(II) by PhSeSePh could be isolated and characterized (Scheme 1B).[6] At higher temperatures, this Pd(IV) complex decomposed to form a carbon–selenium bond-containing product and ethane. The analogous Pd(IV) intermediate from BzOOBz could also be detected by ^{1}H NMR, but was too unstable to be isolated; its decomposition yielded the corresponding oxidation products. In our early work on chiral oxazoline-directed asymmetric β-C(sp^3)–H acetoxylation (Scheme 1C),[7] we proposed that the oxidative addition of AcOO^{t}Bu forms a Pd(IV) intermediate, which undergoes subsequent reductive elimination to afford acetoxylated product. However, despite the great value such reactions might have for synthetic chemistry, in the past decade further efforts to develop C–H activation reactions using peroxides as the sole oxidant have led to little success outside of C(sp^2)–H functionalization reactions.[8] Indeed, the use of peroxides for C–H activation reactions

directed by weakly coordinating native functional groups was unprecedented until our recent disclosure of the β-lactonization of free aliphatic acids (Scheme 1D).[9]

Scheme 1. Pd(IV) Chemistry Enabled by Group 16 Oxidants



Hydroxy fatty acids represent an important class of lipids that have broad applications in dietary supplements and pharmaceuticals.[10] The distance between the hydroxyl and carboxylic acid functional groups has a remarkable effect on biological activity.[11] It is therefore highly desirable to develop synthetic

methods to selectively oxidize parent fatty acids.[12,13] Recent advances in the C(sp^3)–H activation of aliphatic acid derivatives represent a powerful approach to the direct oxidation of aliphatic acids at the β position (Scheme 1C).[7] However, these reaction protocols always require exogenous directing groups (DGs) to promote cyclometallation; thus two or three additional steps are required to install and remove the DG.[4c,7,14,15a-c] Additionally, reported oxidants used in C–H oxidation are largely limited to hypervalent iodine reagents such as $PhI(OAc)_2$.[4,14b-g,15,16] Despite the early successes in β-arylations of free acids through the reactivity of sodium or potassium carboxylates,[2c] analogous acetoxylation reactions were only recently reported by van Gemmeren's group.[16] However, this protocol requires 2.5 equivalents of excess acid substrate and $PhI(OAc)_2$ as the limiting reagent. In addition, aliphatic acids containing α-hydrogens are not reactive. Despite significant advances in developing diverse C–H activation transformations for free aliphatic acids,[17] scalable and practical β-C(sp^3)–H oxidations of free acids remain a significant challenge.

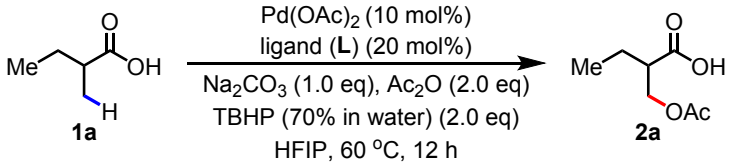
Herein we report β-C(sp^3)–H acyloxylation of free carboxylic acids enabled by a newly developed mono-*N*-protected β-amino acid (MPAA) ligand (Scheme 1D). This method features relatively mild temperatures (60 °C), an inexpensive and practical oxidant (TBHP in water, $5/mol), and uses two equivalents of Ac_2O as the crucial promoter. A broad range of aliphatic acids containing α-hydrogens or α-quaternary centers are compatible with this catalysis. Exclusive mono-selectivity was observed for acids bearing multiple α-methyl groups. The C(sp^3)–H γ-, δ-, and ε-lactonization of free carboxylic acids has also been realized for the first time.

2. Results and Discussion

Following our earlier disclosure of the asymmetric β-acetoxylation of aliphatic acids using chiral oxazoline directing groups,[7] we have extensively investigated the possibility of extending this practically appealing catalytic system to free carboxylic acids without success for the past 15 years. Prompted by our recent discovery that C(sp^3)–H activation of free carboxylic acids could be promoted by a bidentate ligand,[17] we began to test various ligands for reactivity using TBHP (70% in water) as the oxidant. We

discovered that a β-amino acid ligand promoted an unprecedented β-lactonization reaction.[9] This finding prompted us to further tune the ligand and reaction conditions such that the reductive elimination pathway of the Pd(IV) intermediate might favor an acyloxylation pathway (Scheme 1D). We selected 2-methyl butyric acid **1a** as a model substrate for ligand design and reaction development (Table 1). While no desired acetoxylation product was detected in the absence of ligand, we were pleased to observe a 13% ^{1}H NMR yield of β-acetoxylation product **1b** when using the thioether-based bidentate ligand **L2**.[17d] However, thioether ligand **L2** was completely oxidized to sulfoxide after the reaction, which may have contributed to the low yield of the reaction. Guided by MPAA ligand-enabled arylation[17b,c,f] and lactonization[9] reactions of free aliphatic acids, a series of commercially available MPAA ligands (**L4**–**L8**) that are stable in the presence of peroxide were investigated. To our delight, the simple β-amino acid ligand **L8** further improved the yield to 44%. Further modifications to the backbone of the β-amino acid ligand (**L9**–**L11**, with **L10** being the optimal ligand from the previously reported β-lactonization reaction), led to no further improvement in yield. Aiming to test the effect of a more rigid conformation and bite angle on ligand reactivity,[18] a series of cycloalkane-based *cis*-bidentate β-amino acid ligands (**L12**–**L14**) were prepared. To our delight, the yield was improved to 61% using the cyclopentane-based ligand **L12**. Furthermore, the corresponding methyl ester of the desired acetoxylation product could be isolated in 72% yield when using TBHP in decane. However, lower catalysis loading led to lower yield: using 5 mol% and 2 mol% Pd only gave 31% and 7% ^{1}H NMR yield, respectively. A control experiment showed that no reaction occurred in the presence of the γ-amino acid ligand (**L15**), indicating the importance of six-membered chelation for the observed reactivity.

Table 1. Ligand Investigation for β-C(sp^3)–H Acetoxylation[a,b]



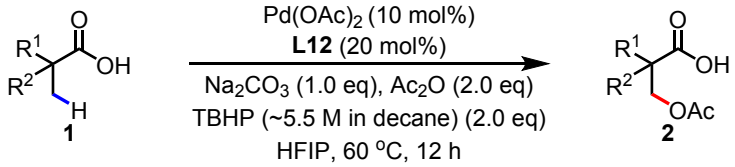
w/o ligand 0%	**L1**, 0%	**L2**, 13%	**L3**, 0%
L4, 25%	**L5**, 29%	**L6**, 18%	**L7**, 28%
L8, 44%	**L9**, 40%	**L10**, 28%	**L11**, 19%
L12, 61%(72%[c])	**L13**, 56%	**L14**, 43%	**L15**, 0%

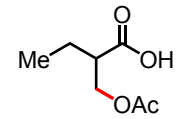
[a]Conditions: **1a** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), ligand (**L**) (20 mol%), Na_2CO_3 (1.0 eq), Ac_2O (2.0 eq), TBHP (70% in water) (2.0 eq), HFIP, 60 °C, 12 h. [b]The yields were determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c]TBHP (~5.5 M in decane) (2.0 eq), isolated yield of the corresponding methyl ester.

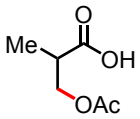
With the optimal ligand and reaction conditions in hand, the scope of aliphatic carboxylic acids was evaluated (Table 2). Compared to the β-lactonization reaction,[9] this protocol showed broader scope since a wide range of aliphatic carboxylic acids containing α-hydrogens were compatible with the current conditions. Commercially available 2-methyl aliphatic acids (**1a**–**1e**) could undergo β-C(sp^3)–H acetoxylation in good yields. Less reactive propionic acid (**1f**) also provided the acetoxylation product in moderate yield (51%). Aliphatic carboxylic acids bearing cyclic rings, including six- (**1g**–**1j**), five- (**1k**), four- (**1l**), and three- (**1m** and **1u**) membered rings, were well tolerated. Among these acids, potentially reactive functional groups including carbonyl (**1h**) and *tert*-butyloxycarbonyl (Boc) (**1j**) groups were untouched under these mild conditions. Phenyl (**2n**–**2p**, **2v**, **2y**, and **2ab**) groups were also compatible

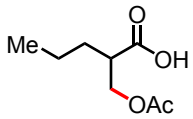
with the TBHP system, and remained intact despite the potentially reactive aryl or benzylic C–H bonds. A range of synthetically versatile functionalities such as benzoyl (Bz) protected hydroxyl (**2q**), ester (**2r**), chloro (**2s**), fluoro (**2w**), and trifluoromethyl (**2x**) were all well tolerated. Aliphatic carboxylic acids bearing α-quaternary centers (**1t**–**1ab**) consistently afforded the desired acetoxylation products in useful yields. Notably, compared to other β-C(sp^3)–H functionalization reactions, this protocol displayed exclusive mono-selectivity (**2b** and **2t**–**2y**) in the presence of two α-methyl groups, likely due to catalysis deactivation *via* bidentate chelation by the installed OAc group and carboxylate group. It is noteworthy that the low yield for several cases is due to low conversion; remaining unreacted acid substrates could be detected from crude ^{1}H NMR, while by-products such as β-lactone and β-hydroxy acid weren't observed during the reaction. Besides acetic anhydride, other aliphatic acid anhydrides including propionic, isobutyric, and pivalic anhydrides are also compatible with the reported protocol but with low efficiency (see Supporting Information Table S7).

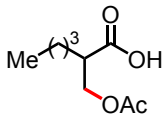
Table 2. Substrate Scope for β-C(sp^3)–H Acetoxylation[a,b]

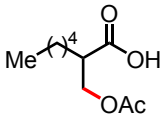


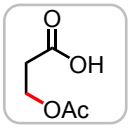

2a, 72%

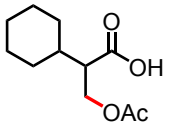

2b, 72%
mono/di > 20/1

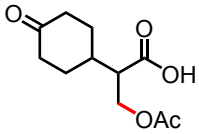

2c, 74%

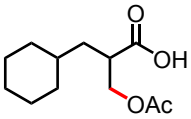

2d, 64%

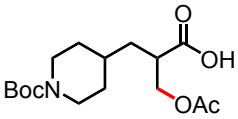

2e, 67%

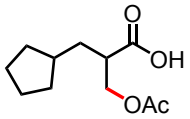

2f, 51%

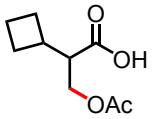

2g, 44%

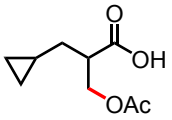

2h, 37%

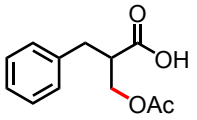

2i, 54%

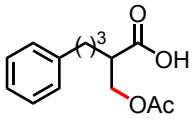

2j, 41%

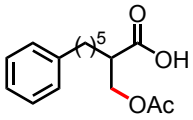

2k, 46%

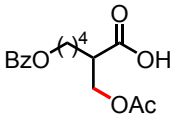

2l, 50%

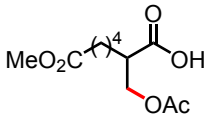

2m, 43%

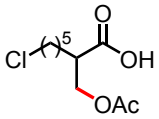

2n, 40%

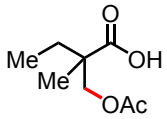

2o, 51%

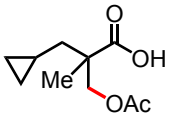

2p, 41%


2q, 66%


2r, 62%


2s, 52%


2t, 45%
mono/di > 20/1


2u, 33%
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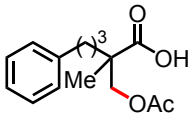
2v, 43%
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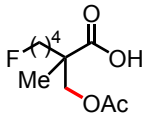
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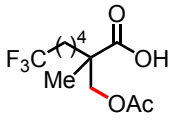
mono/di > 20/1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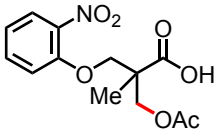
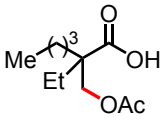
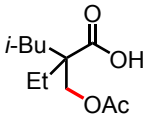
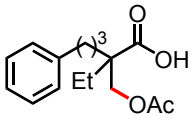

2y, 55%
mono/di > 20/1


2z, 52%

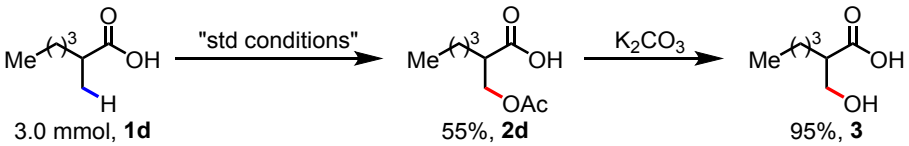

2aa, 54%


2ab, 55%

[a]Conditions: **1** (0.1 mmol), Pd(OAc)$_2$ (10 mol%), **L12** (20 mol%), Na_2CO_3 (1.0 eq), Ac_2O (2.0 eq), TBHP (~5.5 M in decane) (2.0 eq), HFIP, 60 °C, 12 h. [b]Isolated yields of the corresponding methyl ester.

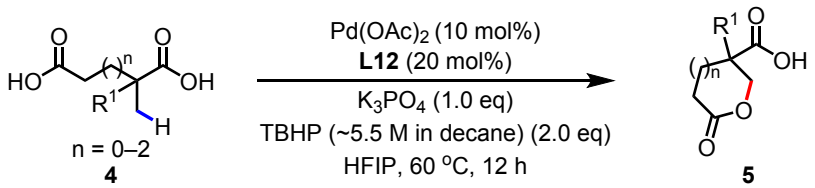
To demonstrate the utility of the herein reported method, we performed the reaction on a 3.0 mmol scale with substrate **1d** using TBHP in water under the aforementioned reaction conditions, yielding the desired β-acetoxylated carboxylic acid in 55% yield. The acetyl protecting group could be removed in the presence of K_2CO_3 to generate the free β-hydroxy acid in near quantitative yield (95%). (Scheme 2)

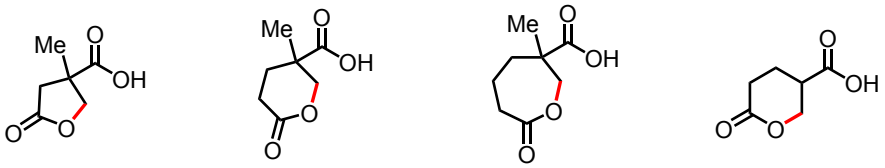
Scheme 2. Scale-up Reaction and Deprotection of Acetyl Group



We were also interested in whether this protocol could be extended to form synthetically valuable lactones in an intramolecular fashion (Table 3). Although a single example of C(sp^3)–H lactonization of acid derivatives has been reported,[14f] this method was limited to the syntheses of γ-lactones and the use of a directing group. By simply changing the base and removing Ac_2O (see Supporting Information for details), we were delighted to find that the desired lactonization product could be obtained. Different sizes of lactones such as γ-lactones (**5a**), δ-lactones (**5b** and **5d**), and ε-lactones (**5c**) could be formed in moderate to good yields. Less reactive free carboxylic acids containing α-hydrogen (**4d**) were also compatible with the standard conditions.

Table 3. Substrate Scope for C(sp^3)–H γ-, δ-, and ε-Lactonization[a,b]

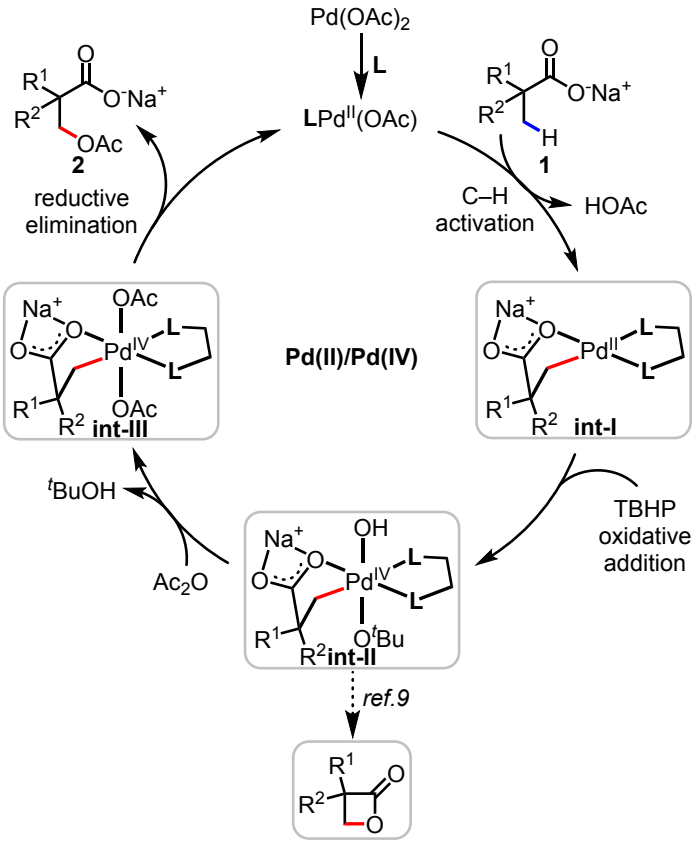




[a]Conditions: **4** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), **L12** (20 mol%), K_3PO_4 (1.0 eq), TBHP (~5.5 M in decane) (2.0 eq), HFIP, 60 °C, 12 h. [b]Isolated yields of the corresponding methyl ester.

Based on previous literature[6-9] and our results from the lactonization reaction, we propose that our transformation proceeds *via* the Pd(II)/Pd(IV) catalytic cycle outlined in Scheme 3. First, coordination of $Pd(OAc)_2$ to an MPAA ligand generates the active **L**Pd(II)(OAc) species. After coordination of the acid substrate **1** to Pd, both the counteranion Na^+ and the MPAA ligand accelerate the cyclopalladation of the β-C(sp^3)–H bond to form **int-I**. Next, oxidative addition of **int-I** by TBHP produces **int-II**. The direct involvement of TBHP without formation of AcO^{t}Bu by Ac_2O in the oxidation addition step is supported by ^{1}H NMR studies of the reaction and the success of lactonization under the conditions without Ac_2O. In the previously reported β-lactonization reaction, promoted by ^{t}BuO$^-$ and MPAA on Pd(IV) center, selective reductive elimination of **int-II** yields strained β-lactone product. In contrast, in this case, **int-II** undergoes subsequent ligand exchange by Ac_2O to generate **int-III**. Finally, reductive elimination generates β-acetoxylation product **2** and regenerates **L**Pd(II)(OAc) species; however, an SN_2-type reaction by AcO$^-$ that affords the final product cannot be ruled out. Similarly, for lactonization reaction, two possible pathways of Pd(IV) center (**int-II**) are proposed to generate lactone product: (1) carboxylic acid moiety on the side chain can replace OH or O^{t}Bu on Pd(IV) (**int-II**) by ligand exchange. Subsequent reductive elimination affords the lactonization product; (2) it is also possible that the other carboxylate from diacid can attack C–Pd(IV) bond of **int-II** by SN_2-type reaction to yield lactone product. The possibility of forming the acetoxylated product from the corresponding β-lactone was ruled out by a control experiment: when the β-lactone analog of **2t** was subjected to the standard conditions, no acetoxylated product was observed.

Scheme 3. Proposed Mechanism for β-C(sp^3)–H Acetoxylation



3. Conclusion

In summary, we have developed Pd(II)-catalyzed intra- and intermolecular C(sp^3)–H acyloxylation of carboxylic acids using inexpensive TBHP as the sole oxidant. The key to this reaction's success hinged on the design of a cyclopentane-based MPAA ligand. The use of the inexpensive oxidant TBHP (70% in water) renders this reaction practical and scalable. A wide range of α-methyl aliphatic carboxylic acids are compatible with the reported conditions and exclusive mono-selectivity is observed in the presence of multiple α-methyl groups. An efficient method for the C(sp^3)–H γ-, δ-, and ε-lactonization of free carboxylic acids has also been realized for the first time.

4. Experimental Section

General procedure for β-C(sp^3)–H acetoxylation. In the culture tube, $Pd(OAc)_2$ (10 mol%, 2.2 mg), ligand **L12** (20 mol%, 3.4 mg), Na_2CO_3 (1.0 eq, 10.6 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), Ac_2O (2.0 eq, 19 μL), and TBHP (~5.5 M in decane) (2.0 eq, 36 μL) were added. The reaction mixture was stirred at rt for 3 minutes, and then heated to 60 °C for 12 hours (600 rpm). After being allowed to cool to room temperature, the mixture was treated with AcOH (0.05 mL) and concentrated *in vacuo*. The resulting mixture was dissolved in MeOH (1.0 mL), treated with $TMSCHN_2$ (2.0 eq), and concentrated *in vacuo* after 1 hour. The crude mixture was purified by pTLC or column chromatography to afford corresponding methyl esters. Full experimental details and characterization of new compounds can be found in the Supporting Information.

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Notes. The authors declare no competing financial interest.

Acknowledgements. We gratefully acknowledge The Scripps Research Institute and the NIH (NIGMS, R01GM084019) for financial support.

Supporting Information Available. Full experimental details and characterization of new compounds. This material is available free of charge via the internet at http://pubs.acs.org.

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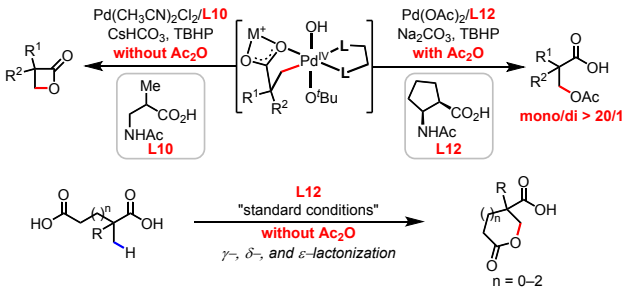
TOC Graphic


Pd(CH3CN)2Cl2/L10
CsHCO3, TBHP
without Ac2O
Pd(OAc)2/L12
Na2CO3, TBHP
with Ac2O
mono/di > 20/1
L10
L12
L12
"standard conditions"
without Ac2O
γ–, δ–, and ε–lactonization
n = 0–2