# Ligand-Enabled Double γ-C(sp³)—H Functionalization of Aliphatic Acids: One-Step Synthesis of γ-Arylated γ-Lactones

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## Abstract

γ-methylene C(sp³)—H functionalization of linear free carboxylic acids remains a significant challenge. Here in we report a Pd(II)-catalyzed tandem γ-arylation and γ-lactonization of aliphatic acids enabled by a L,X-type CarboxPyridone ligand. A wide range of γ-arylated γ-lactones are synthesized in a single step from aliphatic acids in moderate to good yield. Arylated lactones can readily be converted into disubstituted tetrahydrofurans, a prominent scaffold amongst bioactive molecules.

## Graphical Abstract
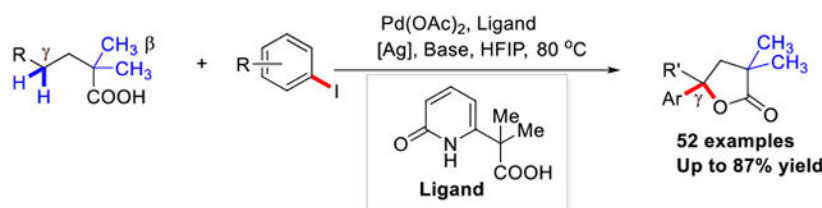


A Pd(II)-catalyzed tandem γ-methylene C-H arylation and lactonization of aliphatic acids was enabled by a L,X-type CarboxPyridone ligand. A wide range of γ-arylated -γ-lactones are synthesized in a single step from aliphatic acids in moderate to good yield. Arylated lactones can readily be converted into disubstituted tetrahydrofurans, a prominent scaffold amongst bioactive molecules.

## Keywords

carboxylic acids; C—H activation; arylation; lactonization; palladium

Lactones are estimated to be present in nearly one-third of natural products and medicinally active molecules.[1] In particular, γ-butyrolactones with a tertiary center adjacent to the oxygen atom are commonly encountered in natural products (Scheme 1.A) and can be used as valuable synthetic intermediates for bioactive targets. For instance, γ-ethyl-

γ-phenyl-butyrolactone (EFBL) exhibits both anticonvulsant and hypnotic properties,[2] various tulipaline A derivatives have shown anticancer effects,[3] while Boivinianin A[4] and 3-hydroxyboivinic acids were found in natural products. Generally, these γ-tertiary arylated γ-butyrolactone derivatives are synthesized from unsaturated carboxylic acids via electrophilic lactonization[5] or hydro lactonization[6]. Therefore, the development of new catalytic methods for the synthesis of arylated γ-butyrolactones from simple starting materials is of high interest in medicinal chemistry. A transition metal catalyzed double γ-C(sp$^3$)—H functionalization of commercially available aliphatic acids would be highly desirable for rapid diverse synthesis of γ-butyrolactones.

Over the past decades following the discovery of MPAA ligands in Pd-catalyzed C—H activation/functionalization, a series of bifunctional ligands have been developed to functionalize inert C(sp$^3$)-H bonds of aliphatic substrates, broadening native substrate scope and enabling new transformations.[7] Aliphatic acids have attracted much attention for the C(sp$^3$)—H functionalization via Pd-catalysis due to their abundant occurrence in bioactive molecules and organic molecules.[8] A series of catalytic systems have been developed for various ligand enabled transformations of terminal *β- or γ*-methyl C(sp$^3$)—H bonds to access a diverse range of reactions. [9-16] Despite these advances, selective activation of methylene C—H bonds over methyl C-H bonds remains challenging, owing to the higher reactivity of the latter towards palladium catalyzed C—H activation reactions. Recently our group developed a series of pyridine-pyridone bidentate ligands[17] that delivered α,β-unsaturated carboxylic acids and γ-alkylidene butenolides via β- methylene C(sp$^3$)—H activation of aliphatic acids.[18,19-22] These findings prompted us to design new catalysts/ligands and reaction conditions[23,24] to achieve the previously inaccessible γ-methylene C(sp$^3$)-H bond functionalization.[25]

In our initial report in 2022, a method for Pd-catalyzed γ-methylene C—H lactonization relied on the use of dicarboxylic acids and a pyridine-pyridone ligand (Scheme 1.B).[26] Recently, we also demonstrated Pd-catalyzed transannular C(sp$^3$)—H arylation of cyclic carboxylic acids using a newly developed quinuclidine-pyridone ligand (Scheme 1.B).[27] However, γ-lactonization was limited to diacids, while γ-C(sp$^3$)—H arylation was achieved for cyclic substrates only. The development of efficient catalysts and strategies to functionalize γ-methylene C(sp$^3$)—H bonds in linear aliphatic acid remains an unanswered challenge.

Herein, we report a tandem γ-C(sp$^3$)—H arylation/lactonization of linear aliphatic acid enabled by an L,X-type CarboxPyridone ligand. A wide range of free aliphatic acids could be converted to γ-arylated γ-lactone products with high yields and mono-selectivity using various aryl iodides as coupling partners. The γ-arylated γ-lactones can also be used as a key synthetic precursor to access medicinally significant disubstituted tetrahydrofuran derivatives. [28]

We started our investigation by using 2,2-dimethyl pentanoic acid (**1a**) as a model substrate and 4-iodobiphenyl as a coupling partner[29] for the identification of suitable ligands and conditions (Table 1). In the absence of any external ligand, only β-methyl C(sp$^3$)—H arylation was observed. Monoprotected amino acids (MPAA) (**L1**), mono-protected

aminoethyl phenyl thioether (MPAThio) (**L2**) and monodentate pyridone (**L3**) ligands also resulted in only β-methyl C(sp$^3$)―H arylation and failed to give any methylene functionalized product. We then turn to the recently discovered pyridine-pyridone ligand class. Employment of ligand **L4** that forms 5-membered chelation was unsuccessful and resulted in β-methyl C(sp$^3$)―H arylation only. Encouragingly, switching to the six-membered chelating bidentate pyridine-pyridone ligand **L5** afforded 6% yield of the desired double γ-C(sp$^3$)―H arylation/lactonization product. These observations indicate that ligands play a key role in controlling the regioselectivity between the β-methyl and γ-methylene C―H bonds. A slight improvement was seen with **L6** and **L7** ligands, producing the desired products in 10% and 24% yields respectively. To our delight, the quinoline-pyridone ligand (**L8**) further improved the yield to 64%. 5-chloro ligand (**L10**) showed comparable results with **L8**. While increasing the steric bulk at the methylene junction was not fruitful (**L9 & L11**) and resulted in a drop of yield. Introducing a chloro substituent at the 6-position of the pyridine ring in the ligand (**L12**) further improved the yield to 71%. Our recently developed quinuclidine-pyridone ligand[27] (**L13**) for γ-C(sp$^3$)―H arylation of cyclic acids was also tested, albeit affording poor yield.

Surprisingly, we found that CarboxPyridone ligand (**L14**) (which enabled *ortho* C―H activation and hydroxylation of a broad range of benzoic and phenylacetic acids[30]) was uniquely effective in improving both the yields and the scope of the coupling partners. Increasing to 15 mol% loading of the ligand resulted in further improvement and gave the optimum reaction conditions (89% yield). Further modification of the CarboxPyridone ligand backbone (**L15**) resulted in lower yield of desired product.

With the optimal ligand and reaction conditions in hand, we then explored the generality of this tandem γ-C(sp$^3$)―H arylation/ lactonization by varying the structure of the linear carboxylic acid with 4-iodobiphenyl as the coupling partner (Table 2). A wide range of α-quaternary aliphatic carboxylic acids were compatible with the current reaction conditions. Linear aliphatic acids bearing various chain lengths ranging from 5, 6, 7 up to 20 (**1a** to **1k**) were well tolerated with excellent yield and selectivity. The length of the aliphatic chain in the carboxylic acid does not affect the selectivity and yield of the reaction. Chloro substituents at the aliphatic chain (**1l & 1m**) and branched chain substrates (**1n**) were also well tolerated. Whilst substrates containing arene ring at the γ-position of the aliphatic chain (**1o & 1p**) worked with modest yields, substrates with more distant arene substituents (**1q** to **1t**) afforded desired product in good to excellent yield. In case of 1a & 1p minor amounts of γ-lactone products observed without arylation. To show case the utility a marketed drug Gemfibrozil (**1u**) was tried under the reaction condition giving the desired product with modest yield. Variation of the alkyl substituent at the *α*-position (**1v & 1w**) also afforded the γ-arylated γ-lactone products with excellent yield and selectivity.

Interestingly, 2,2-dimethylbutanoic acid bearing primary γ-C―H bonds showed no reaction under the developed condition leaving only unreacted starting material in the reaction medium, suggesting high selectivity of the developed system towards γ-methylene C―H bond over γ-methyl C―H bond. Substrate with two different substituents at the alpha position (**1y & 1z**) was also found viable to give γ-arylated γ-lactone products with good yield. We then performed the reaction on carboxylic acids containing an α-hydrogen. Only

γ-arylated γ-lactone products were observed for 2-methylpentanoic acid (**1aa**) and valeric acid (**1bb**) in 15% and 9% yields respectively. The low yields of these substrates were probably due to the absence of Thorpe-Ingold effect.

Next, a wide range of aryl iodide coupling partners were tested in our arylation/lactonization reaction using 2,2-dimethyl pentatonic acid as a model substrate (Table 3). Employment of unsubstituted iodobenzene afforded 72% yield of the desired product (**4a**). Various aliphatic substituents at the 3- and 4-positions of the aryl iodide provided excellent selectivity and good yield of the γ-arylated γ-lactone products. Halogen substituted aryl iodides including fluoro, chloro and bromo substituents showed good compatibility, with latter particularly useful for subsequent diversification via cross coupling reaction. A range of electron-donating (OMe & OPh) and electron-withdrawing (NHAc, CHO, $CO_2Me$, $NO_2$) substituents were well tolerated. Free hydroxy groups on the aryl iodides are also well tolerated under the reaction conditions to deliver the product (**4t** & **4u**) without affecting the hydroxy group. 2-naphthyl iodide also works perfectly under the developed condition. 2-methoxy substituted aryl iodide gave the desired γ-arylated γ-lactone product (**4ab**), however, it required a higher catalyst loading.

To showcase the utility of these reactions, a larger scale reaction (1.0 mmol scale) was carried out with 80% isolated yield of the desired product (Scheme 2). This γ-arylated γ-lactone can be readily converted to disubstituted tetrahydrofuran in a single step using Lithium Aluminum hydride (LAH) as a reducing agent. This substituted tetrahydrofurans are very important scaffolds in various natural products and medicinally significant molecules. [28]

To investigate the mechanism of this Pd-catalyzed tandem γ-C($sp^3$)—H arylation/lactonization reaction, several control experiments were conducted (Scheme 3). First, no reaction was observed in absence of aryl iodide, which indicates the crucial role of the aryl iodide. Then several possible intermediates as substrates were subjected to the reaction conditions. 4% yield of the desired γ-arylated γ-lactone was obtained from γ-arylated acid **6a,** and no reaction occurred with γ-butyrolactone **6b**, suggesting that neither of those intermediates were likely to be involved in the catalytic cycle. On the other hand, β,γ-dehydrogenated intermediate **6c** & γ-arylated β,γ-dehydrogenated intermediate **6d** gave 23% & 28% yield of the desired product under the developed reaction conditions indicating their potential involvement as intermediate in the reaction. γ,δ-dehydrogenated intermediate **6e** resulted in only 5% yield of the desired product with 30% yield of the corresponding di-isomer, implying that γ,δ-dehydrogenation pathway is unlikely. We have performed another control experiment in presence of 20 mol% **6c** as additive (Scheme 3C) and observed only 4% yield of the desired product, which might have resulted from catalyst inhibition by the excess olefine.[18]

To get more insight into the mechanistic details of the reaction, we have conducted H/D exchange experiments under standard conditions (Scheme 4). In the absence of aryl iodide, we observed 40% deuteration at the methyl C—H bonds of **1a** but no deuterium incorporation on methylene C—H bonds, which means that a reversible β-methyl C—H activation is taking place under these conditions (Scheme 4.A).

Similarly, in the presence of aryl iodide, we also observed 62% deuteration at the methyl C—H bonds, while no deuteration was observed at the β-methylene C—H bonds. These results suggest that the (1) the methyl C—H activation was reversible, but it fails to generate any product under the standard reaction conditions; (2) whereas methylene C—H activations seems irreversible and as soon as C-H activation occurs it converted to product. In another interesting experiment, we performed a reaction with a substrate containing 52% deuteriation (52% deuterium for each β-methylene C—H bond) at the β-methylene C—H and observed that two β-methylene C—H bonds contain 45% and 7% D respectively (Scheme 4.C). These results suggest that the β,γ-dehydrogenation may be acting as a transient intermediate as we didn't observe any dehydrogenated product in our reaction at any time interval (for details see SI).

In summary, we have developed a Pd(II)-catalyzed tandem γ-C(sp$^3$)—H arylation and γ-lactonization of linear aliphatic acids. The key to the success of this reaction is the use of the bidentate CarboxPyridone ligand. This new reaction enables diverse synthesis of γ-arylated γ-butyrolactones from the simple carboxylic acids in a single step. The scalability and compatibility of this transformation with many functional groups make it suitable for synthetic applications. These γ-arylated γ-butyrolactone products can be readily converted to a wide range of disubstituted tetrahydrofuran derivatives.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

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(29). In our reaction, we chose 4-iodo-1,1'-biphenyl as a model aryl iodide since it gives good yield to the desired product and all the characteristic 1H NMR peaks for arylated lactone products are well distinguished to monitor the reaction.

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**A. γ-Arylated γ-Lactone Containing Bioactive Molecules and Natural Products**

EPBL

Tulipaline A derivatives

PDE-IV Inhibitors

Boivinianin A

3-hydroxyboivinianic acid

Grandilodines C
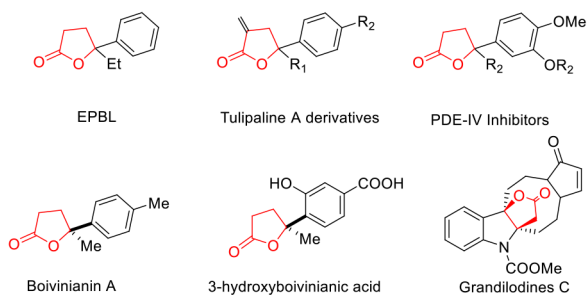
**B. Pd(II)-Catalyzed γ-Methylene C-H Functionalization of Free Aliphatic Acid**

γ−Lactonization of diacids

γ−Lactonization
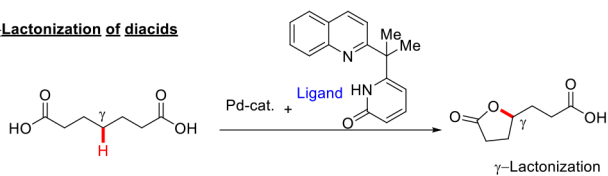
γ-Arylation of Cycloalkanecarboxylic Acids:

γ−Arylation

**C. Double γ− C(sp³)-H Functionalization**
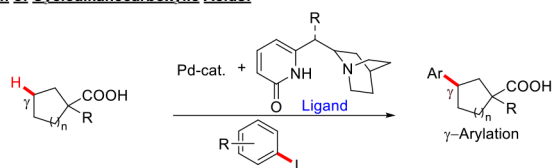
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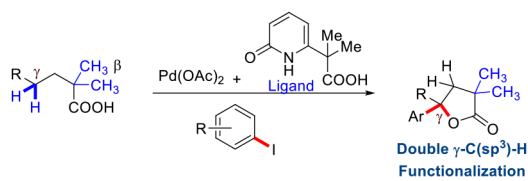
**Scheme 1.**
Pd(II)-Catalyzed γ-Methylene C—H functionalization of Aliphatic Acids
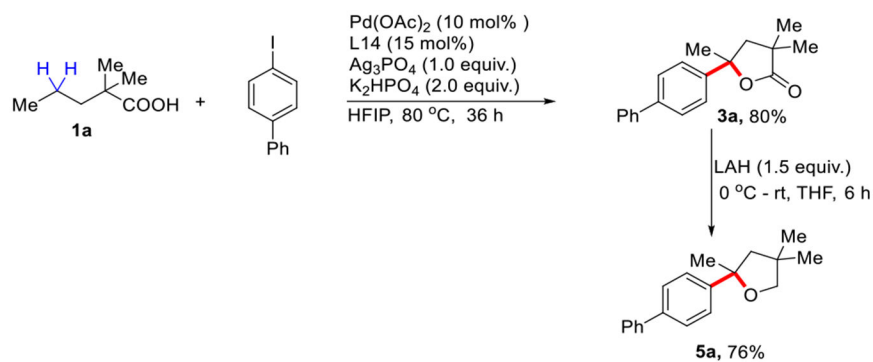
**Scheme 2.**

1.0 mmol Scale Synthesis and Further Transformation to Tetrahydrofuran. Step-1: Conditions: **1a** (1.0 mmol), **2a** (2.5 equiv.), Pd(OAc)$_2$ (10 mol %), ligand L14 (15 mol%), K$_2$HPO$_4$ (2.0 equiv.), Ag$_3$PO$_4$ (1.0 equiv.), HFIP (1.0 mL), 80 °C, under air, 36 h. Step-2: **3a** (0.5 mmol), LAH (1.5 equiv.), THF, 0 °C - rt, 6h.
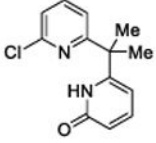
**Scheme 3.**

Control Experiments with Possible Intermediate.
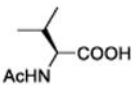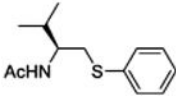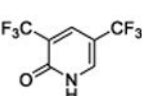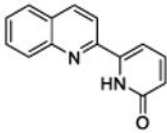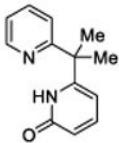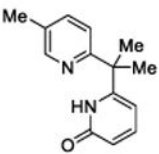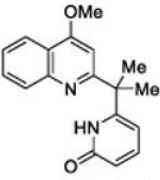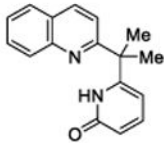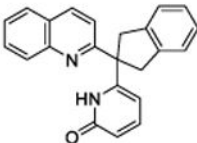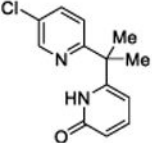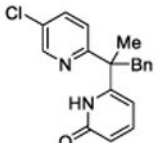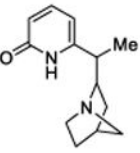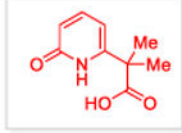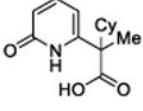
[a] Standard conditions: **1a** (0.1 mmol), 4-Iodobiphenyl (2.5 equiv.), Pd(OAc)$_2$ (10 mol %), L14 (15 mol%), K$_2$HPO$_4$ (2.0 equiv.), Ag$_3$PO$_4$ (1.0 equiv.), 4-Iodobiphenyl (2.5 equiv.), HFIP (1.0 mL), 80 °C, under air, 36 h. Here, Ar means 4-biphenyl group.

**A. Deuterium Experiment in Absence of ArI:**

Pd(OAc)$_2$ (10 mol%)
L14 (15 mol%)
Ag$_3$PO$_4$ (1.0 equiv.)
K$_2$HPO$_4$ 2.0 equiv.)
**HFIP-OD**, 80 °C, 36 h

40% D
40% D
No D
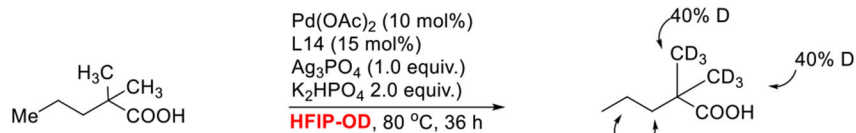
**B. Deuterium Experiment Under Standard Reaction Condition:**

Pd(OAc)$_2$ (10 mol%)
L14 (15 mol%)
Ag$_3$PO$_4$ (1.0 equiv.)
K$_2$HPO$_4$ (2.0 equiv.)
4-I-Biphenyl (2.5 equiv.)
**HFIP-OD**, 80 °C, 36 h

No D
62%D
62%D
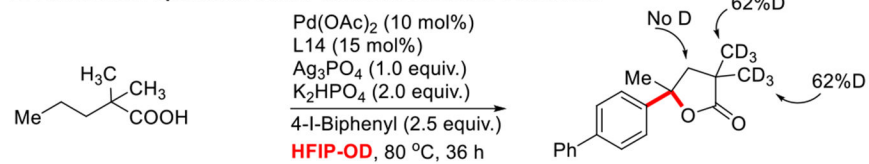
**C. Deuterium Experiment with β-Deuterated Starting Material:**

89% D
89% D
52% D
52% D

Pd(OAc)$_2$ (10 mol%)
L14 (15 mol%)
Ag$_3$PO$_4$ (1.0 equiv.)
K$_2$HPO$_4$ (2.0 equiv.)
4-I-Bipheny (2.5 equiv.)
**HFIP**, 80 °C, 36 h

7% D
45% D
25% D
25% D
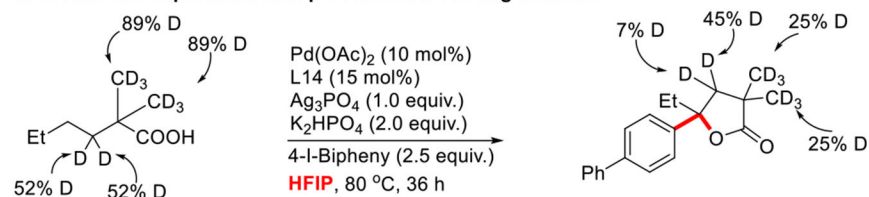
**Scheme 4.**
H/D Exchange Experiments.

**Table 1.**

Ligand Identification*a*:



*[a]*Conditions: **1a** (0.1 mmol), **2a** (2.5 equiv.), Pd(OAc)$_2$ (10 mol %), ligand (10 mol%), K$_2$HPO$_4$ (2.0 equiv.), Ag$_3$PO$_4$ (1.0 equiv.), HFIP (1.0 mL), 80 °C, under air, 36 h. 20 mol% ligand used for L1 and L3. Here, Ar indicates 4-biphenyl group. $^1$H NMR yields, determined using CH$_2$Br$_2$ as an internal standard.

*[b]*15 mol% ligand loading.

*[c]*isolated yield.

**Table 2.**

Scope for the γ-Arylation/Lactonization Reaction[a]:





3a, 83%    3b, 65%    3c, 62%    3d, 55%

3e, 69%    3f, 52%    3g, 62%    3h, 60%

3i, 56%    3j, 72%    3k, 71%    3l, 55%

3m, 26%[b]    3n, 79%    3o, 38%[b,c]    3p, 28%[b,c]

3q, 50%    3r, 45%    3s, 77%    3t, 80%

3u, 25%[d]    3v, 66%    3w, 80%    3x, No reaction

3y, 75% (dr: 1.5:1)    3z, 73% (dr: 1.3:1)    3aa, 15% (dr: 1.5:1)    3bb, 9%
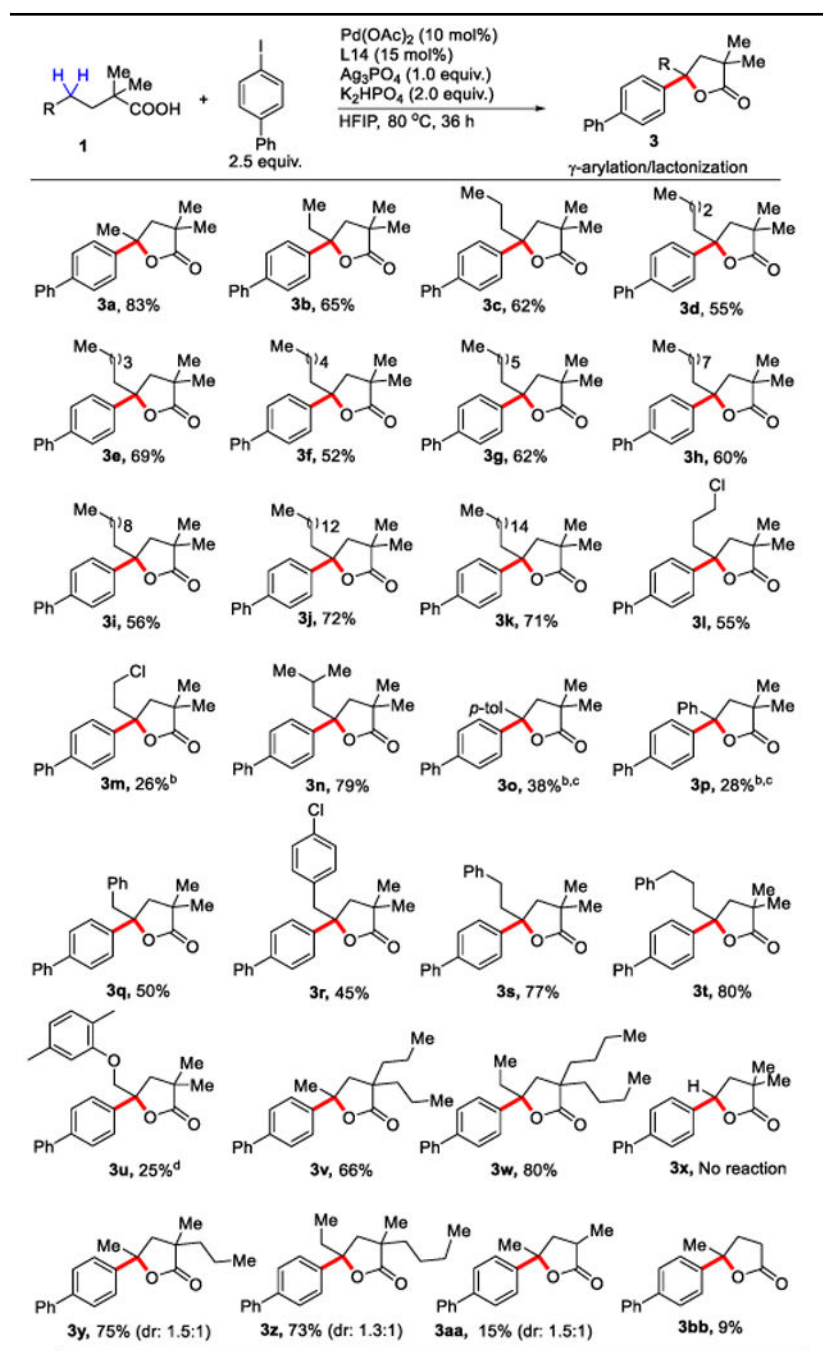
[a]Conditions: **1a** (0.1 mmol), **2a** (2.5 equiv.), Pd(OAc)$_2$ (10 mol %), ligand 14 (15 mol%), K$_2$HPO$_4$ (2.0 equiv.), Ag$_3$PO$_4$ (1.0 equiv.), HFIP (1.0 mL), 80 °C, under air, 36 h.

[b]20 mol% Pd(OAc)$_2$ & 20 mol% ligand used.

[c] in case of 3o and 3p 6% and 4% respectively lactonized products obtained without arylation observed.

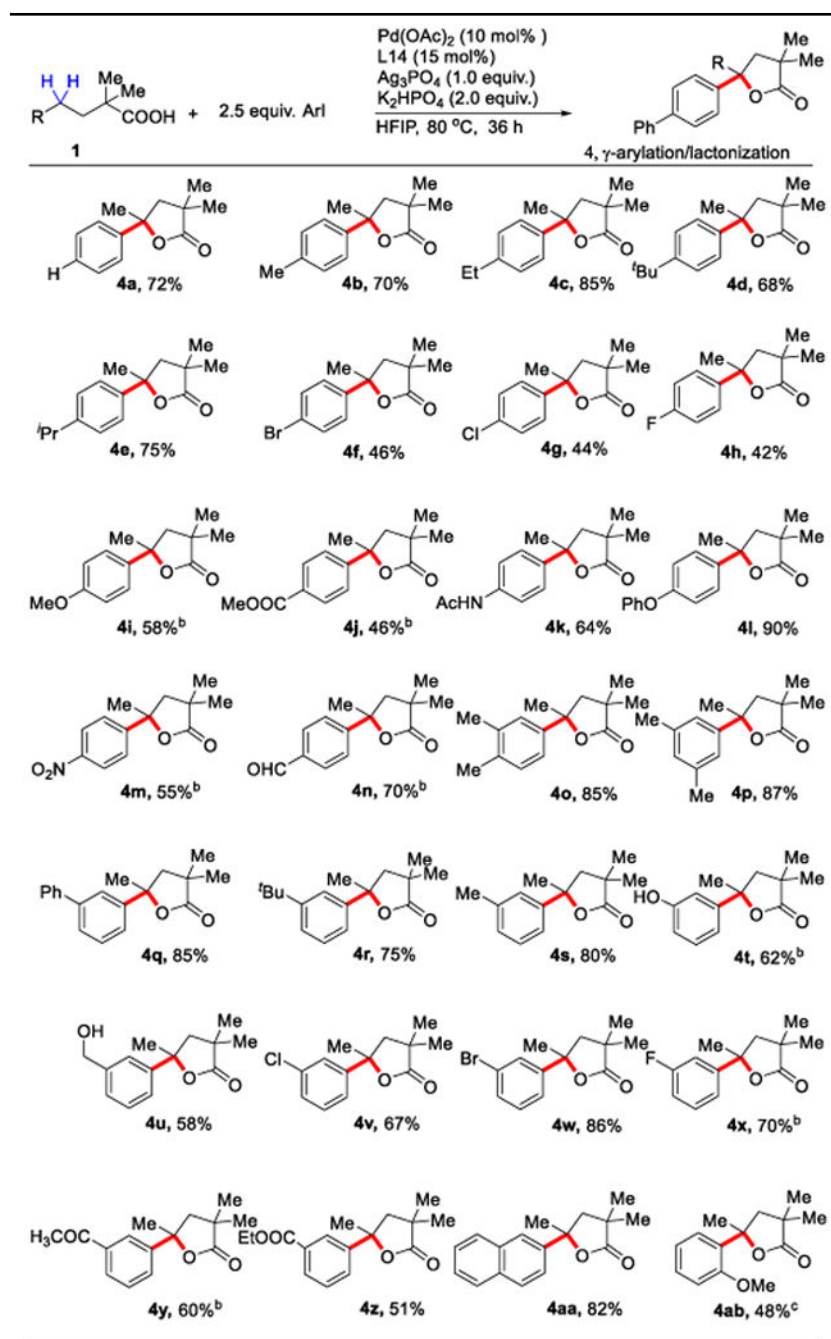[d] 30 mol% Pd(OAc)$_2$ & 30 mol% ligand was used. The diastereomeric ratio was determined from crude NMR analysis.

**Table 3.**

Aryl Iodide Scope for the γ-Arylation/Lactonization Reaction[a]:

[c] 30 mol% Pd(OAc)2 & 30 mol% ligand was used.