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A direct route to six and seven membered lactones via γ -C(sp³)-H activation: a simple protocol to build molecular complexity†

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Lactones comprise a class of valuable compounds having biological as well as industrial importance. Development of a methodology to synthesize such molecules directly from readily available materials such as aliphatic carboxylic acid is highly desirable. Herein, we have reported synthesis of δ -lactones and ϵ -lactones via selective γ -C(sp³)-H activation. The γ -C-H bond containing aliphatic carboxylic acids provide six or seven membered lactones depending on the olefin partner in the presence of a palladium catalyst. A mechanistic investigation suggests that C-H activation is the rate-determining step. Further transformations of the lactones have been carried out to showcase the applicability of the present strategy.

Introduction

Lactones are an integral part of biological systems as well as industrially important moieties.¹ Lactone motifs are abundantly present as small molecule signaling agents in different organisms.² In particular, six and seven membered lactones are flavor and aroma constituents in many natural products.³ The wide availability and functional group interconversion ability of carboxylic acids makes them an excellent contender to synthesize lactones.⁴

Transition metal catalyzed C-H bond activation has evolved as one of the most efficient tools to transform readily available materials into value added commodity chemicals.⁵ The last few decades have witnessed tremendous growth in the use of aromatic carboxylic acids as a substrate in C-H functionalization reactions.⁶ A similar success story has also been witnessed for aliphatic carboxylic acids with assistance from an exogenous template.⁷ But use of external templates decreases the efficiency of these protocols in terms of step as well as atom economy. Although, a few reports of directing group free reactions of aliphatic carboxylic acids are known, most are restricted to the proximal β position.⁸ This is due to formation of a favorable five membered metallacycle during β -C(sp³)-H activation. Moving towards further remote positions would require formation of

less preferred metallacycles with the assistance from weakly coordinating carboxylates, which presents a significant challenge. Very recently, we have demonstrated the arylation reaction on such a free aliphatic carboxylic acid at the remote γ -position.⁹ Shi and coworkers have also contributed immensely in this area of aliphatic C-H functionalization.¹⁰

The Yu group reported β -olefination of aliphatic acids^{8d} and γ -olefination using a highly acidic *N*-aryl amide auxiliary.^{7b} However, this γ -olefination requires preinstallation of an expensive *N*-aryl amine template and removal of the auxiliary post functionalization, which limits its synthetic utility. In 2017, we faced the same problem while using an 8-amino quinoline template for γ -C(sp³)-H olefination.^{7f}

We, therefore, strived to develop a methodology which can promote olefination without using any exogenous auxiliary. A γ -C(sp³)-H olefination of free aliphatic acids enabled by an acetyl protected amino acid ligand has been developed here (Fig. 1). δ -Lactones were formed as the products of γ -C(sp³)-H olefination via subsequent C-H activation/C-O cyclization. Considering the challenges in developing Heck coupling reactions with alkyl halides,¹¹ direct olefination with readily available carboxylic acids would be highly useful. While we were preparing this manuscript, the Gemmeren¹² and Yu¹³ groups reported similar approaches.

Results and discussion

We started to inspect the γ -C(sp³)-H olefination reaction with 3,3-dimethyl butanoic acid as the model substrate and benzyl acrylate as the olefin partner. An inorganic counter cation such as an alkali metal (Na⁺, K⁺, Cs⁺ etc.) plays a pivotal role in transformation of carboxylic acid containing substrates. Such counter cations facilitate C-H activation by binding with

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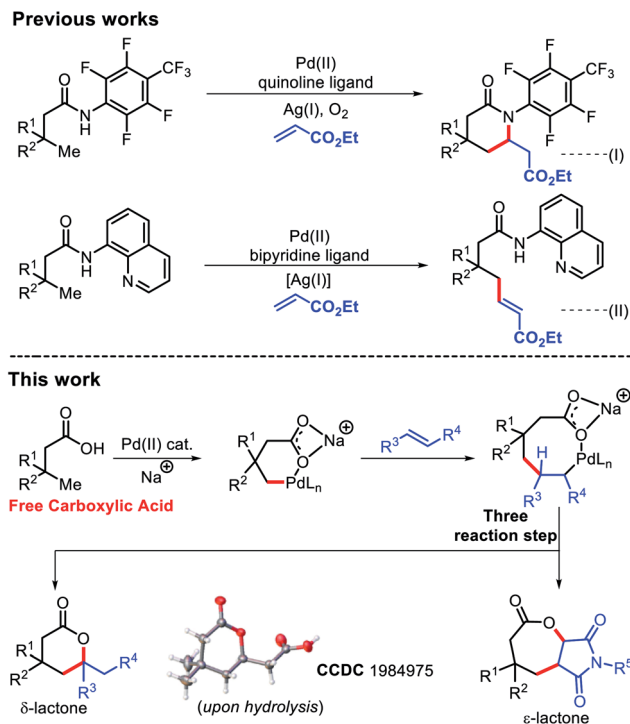
Fig. 1 γ -C(sp³)-H olefination of a carboxylic acid derivative.

Fig. 2 Initial reaction conditions.

a carboxylate in a κ^2 coordination mode and thus Pd gets the opportunity to activate the accessible C-H bonds. A combination of Pd(OAc)₂ (10 mol%), 2-pyridone (20 mol%), Ag₂CO₃ (2 equiv.), and Na₂CO₃ (1 equiv.) in the presence of 3,3-dimethylbutanoic acid and benzyl acrylate provided 28% isolated yield of **1a** (Fig. 2).

Encouraged by this outcome, we started optimization by varying different Pd salts. Among them Pd(TFA)₂ was found to be the best catalyst (see the ESI[†]). To increase the efficiency of the reaction, we turned our attention towards finding a suitable ligand. We initially investigated pyridine and quinoline based ligands, but found them to be ineffective. Although pyridone ligands were superior, yields were not synthetically useful (Fig. 3).

Employment of phenanthroline and phosphine-based ligands also remained ineffective. We then moved to employ mono-protected amino acids as ligands for the reaction. Although, Boc and Cbz protected amino acids did not show much promise, acetyl protected amino acids increased the yields significantly. Further studies with various acetyl protected amino acids revealed *N*-acetyl valine (**L12**) to be the best ligand with yield up to 91% (NMR yield, Fig. 3). We found an



Fig. 3 Ligand optimization.

alkali metal base to be indispensable for the reaction. Na₂HPO₄ was found to be the suitable base and Ag₂CO₃ (2 equiv.) is the superior oxidant for the reaction. An extensive assessment of the reaction parameters revealed the optimum conditions, which are to treat 3,3-dimethylbutanoic acid (1 equiv.) with benzyl acrylate (1.5 equiv.) in the presence of Pd(TFA)₂ (10 mol%), *N*-Ac-Val (20 mol%), Ag₂CO₃ (2 equiv.), and Na₂HPO₄ (1 equiv.) in HFIP solvent for 12 h at 120 °C to obtain **1a** in 91% yield.

Having the optimal conditions for γ -C(sp³)-H olefination to form six membered lactones, we first explored the scope of aliphatic acids. To our delight, even when we performed the

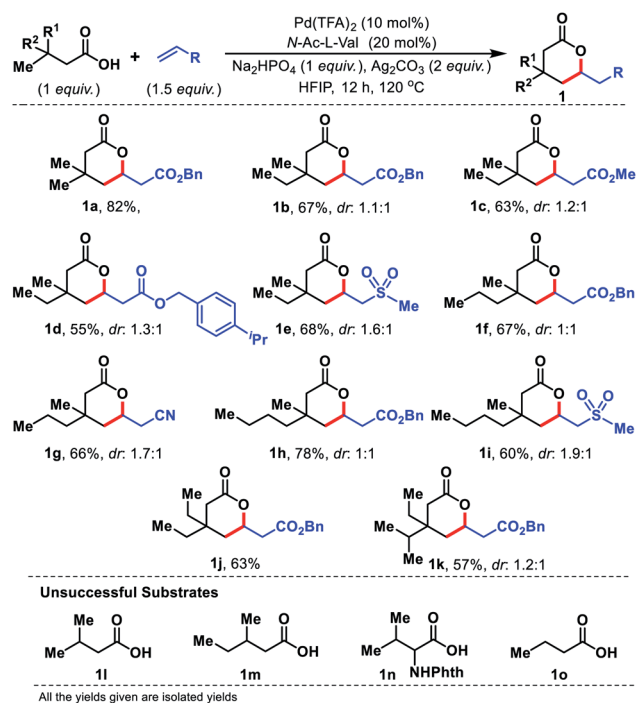


Fig. 4 Diversification of free carboxylic acids.



reaction in the presence of ethyl (**1b–1e**), propyl (**1f** and **1g**), and butyl (**1h** and **1i**) substituents at the β -position of the substrate, the reaction worked efficiently (Fig. 4). Carboxylic acids containing β -diethyl (**1j**) and ethyl-isopropyl (**1k**) substituents were also well compatible. Such substrates work well even when we changed the coupling partner from acrylates to sulphones or acrylonitrile. The β -quaternary center of the acid is necessary for this reaction as it provides a suitable geometrical alignment (*via* the Thorpe–Ingold effect) to form a thermodynamically less stable six membered palladacycle. Acids such as **1l–1o** were unsuccessful under the present reaction conditions.

Next, we diversified the scope of olefin coupling partners. Various substituted benzyl acrylates were explored. Diverse electronic substitutions on the phenyl ring of benzyl acrylate did not affect the efficiency of the protocol (**2a–2j**). A phenethyl acrylate has also been utilized as the olefin coupling partner for γ -C(sp³)-H olefination (**2k**). Other aliphatic acrylates starting from simple methyl acrylate to bicyclic acrylate provided excellent yields under the reaction conditions (**2l–2q**). Long chain acrylates like dodecyl, dodecafluoro acrylate and docosyl acrylate were also found to be suitable coupling partners for this reaction (**2r–2t**) (Fig. 5).



Fig. 5 Scope of various olefins.



The present strategy is not limited to esters of acrylic acid but various activated olefins can also be utilized in the reaction. Olefins containing sulphone, nitrile, ketone and diester groups were well compatible with the reaction conditions and provided corresponding δ -lactones in good to excellent yields (**2u–2ab**) (Fig. 5).

Maleimides are known in the literature as an excellent olefin coupling partner.¹⁴ Various *N*-substituted maleimides possess biological activities, especially antifungal properties¹⁵ which make them a valuable coupling partner in the reaction. We sought to utilize maleimides as the olefin partner in our protocol. To our surprise, such maleimides provided fused seven membered lactones under the present reaction conditions. Initially, we started to explore the seven membered lactone with *N*-alkyl maleimides (Fig. 6, **3a** and **3b**). To evaluate further, various *N*-aryl substituted maleimides were tested and all of them provided seven membered lactones (**3c–3f**). The fused seven membered lactones obtained are prevalent structural motifs in bioactive molecules. Moreover, synthesis of such seven membered lactones *via* γ -C(sp³)-H activation provides a straightforward and effective route compared to traditional methods of synthesizing similar molecules.

To probe the mechanism of the olefination with aliphatic acids, we first tested the relevance of the substrate-palladium species **A** (Fig. 7). We found that **A** is a catalytically and kinetically competent intermediate. A reversibility experiment of the substrate (3,3-dimethyl butanoic acid) in the presence of D₂-HFIP showed no deuterium scrambling in the recovered carboxylic acid. To confirm further, a reversibility experiment was carried out with the deuterated substrate. No deuterium depletion was observed in the recovered substrate. This indicated the irreversible nature of the C–H activation step. The order with respect to the acid and olefin was studied. A first order dependency with respect to the acid and a 0.4 order dependency with respect to the olefin was determined which indicates that only the acid is likely to be involved in the rate determining step of the reaction. The order with respect to the catalyst was found to be nearly unit order (0.86, Fig. 7) which again indicates a similar interpretation.¹⁶ Further information was obtained by the measurement of the kinetic isotope effect (KIE). An apparent KIE value of 2.3 suggests that cleavage of the C–H bond is involved in the rate-determining step of the reaction.



Fig. 6 Scope of maleimides.



Fig. 7 Mechanistic investigation.

Based on the evidence we obtained from the aforementioned experiments and related literature reports,¹⁷ we propose a reaction mechanism in Fig. 8. The carboxylate group of the substrate first binds to the metal catalyst to form a metal coordinated complex **A** which upon treatment with an alkali metal base generates a γ -C–H activated six membered intermediate **B**. Next, olefin binding to **B** and 1,2-migratory insertion lead to an eight membered cyclo-palladated intermediate **D**. From **D**, β -hydride elimination affords **E** which upon reductive elimination followed by Michael addition forms a six or seven membered lactone (Baldwin's rules). The formed Pd(0) oxidized to Pd(II) aided by Ag(I) and completed the catalytic cycle. The reason for the formation of seven membered lactones we believe lies in the cyclization step after reductive elimination. The more substituted position of maleimide disfavors the cyclization and therefore, cyclization occurred at the less substituted side of maleimide to form the seven membered lactone.¹⁸

The practicality of the reaction has been demonstrated by performing the reaction up to the gram scale (see the ESI†). The decrease in yield on a large scale is perhaps due to improper





Fig. 8 Mechanistic cycle.

heat and mass transfer in a bigger flask. Homogeneity could be an additional issue here. To further harness the utility of the six membered lactones, it has been transformed into structurally different synthons. Reduction with LiAlH_4 provided 1,5,7-triol (**4e**). Selective hydrolysis of the ester group with HCl generated another δ -lactone with a carboxylic group (**4a**). Upon hydrolysis with NaOH an unsaturated pimelic acid derivative was formed (**4b**, **4c**), which was further reduced to its saturated analogue (**4f**) that is widely used for industrial application. The dicarboxylic acid (**4f**) has been cyclized to generate an eight membered anhydride upon treatment with SOCl_2 (**4g**). In a similar fashion,

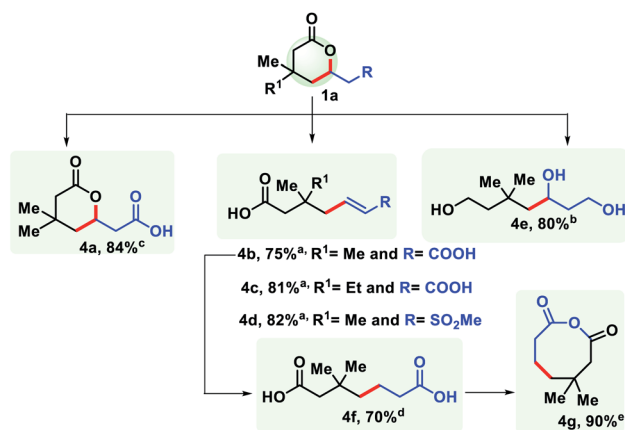


Fig. 9 Side product formation and synthetic applications of δ -lactones. ^a Condition A: **1a** (0.2 mmol), NaOH (4 equiv.), EtOH/ H_2O reflux, overnight. ^b Condition B: **1a** (0.2 mmol), LiAlH_4 (3 equiv.), THF, rt, 12 h. ^c Condition C: **1a** (0.2 mmol), 6N HCl, 12 h, rt. ^d Condition D: **4b** (0.1 mmol) Pd/C (10 mol%), H_2 , MeOH, rt, 12 h. ^e Condition E: **4f** (0.1 mmol), SOCl_2 (3 equiv.), 8 h, rt.

a sulphone containing δ -lactone was hydrolysed to form an unsaturated carboxylic acid (**4d**) (Fig. 9).

Conclusion

In conclusion, a ligand enabled $\gamma\text{-C}(\text{sp}^3)\text{-H}$ olefination protocol has been developed for aliphatic free carboxylic acids. The potential of the methodology has been showcased *via* synthesis of δ -lactones that contain ester, ketone, sulphone, and nitrile groups. Various *N*-substituted maleimides have been utilized to form fused seven-membered lactones. A mechanistic investigation has been carried out to shed light on the reaction mechanism. Further, the application potential of the δ -lactones has been demonstrated through various transformations. Considering the severe challenges involved in developing analogous Heck coupling reactions, this transformation provides an exciting complementary pathway.

Conflicts of interest

There are no conflicts to declare.

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