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Ligand-Enabled β -C(sp³)-H Olefination of Free Carboxylic Acids

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Abstract

An acetyl-protected aminoethyl phenyl thioether has been developed to promote C(sp³)-H activation. Significant ligand enhancement is demonstrated by the realization of the first Pd(II)-catalyzed olefination of C(sp³)-H bonds of free carboxylic acids without using an auxiliary. Subsequent lactonization of the olefinated product *via* 1,4 addition provided exclusively mono-selectivity in the presence of multiple β -C-H bonds. The product γ -lactone can be readily opened to give either the highly valuable β -olefinated or γ -hydroxylated aliphatic acids. Considering the challenges in developing Heck couplings using alkyl halides, this reaction offers a useful alternative.

Graphical Abstract

Carboxylic acids are readily available and highly versatile starting materials in organic synthesis. In the past decade, a number of directed C(sp³)-H activation reactions of aliphatic acids using various directing groups have provided unprecedented synthetic disconnections.¹ For example, Pd-catalyzed C(sp³)-H iodination^{1a}, oxygenation,^{1b} arylation,^{1c} alkylation,^{1d-f} and fluorination^{1g, 1h} have been developed using various directing auxiliaries. However,

carboxyl-directed C(sp³)-H activation reactions are rare. K₂PtCl₄-catalyzed or mediated carboxyl-directed lactonization of aromatic and aliphatic acids has been demonstrated, albeit in poor yields.² The use of COOK salts led to the discovery of Pd-catalyzed C(sp³)-H arylation of free carboxylic acids³ and was further improved by ligand acceleration (eq 1).^{4, 5} However, further development of carboxyl-directed C(sp³)-H functionalization reactions have only been successful using exogenous auxiliaries. In particular, the development of a C(sp³)-H olefination reaction protocol would be synthetically useful considering the challenges of developing Heck couplings with alkyl halides due to premature β -hydride elimination.⁶ To date, only three precedents using auxiliaries have been reported.⁷ These reactions suffer from the undesired subsequent cyclization reaction with the nitrogen containing auxiliary, preventing further synthetic elaborations.

Herein we report the first example of β -C(sp³)-H olefination of free carboxylic acids enabled by an acetyl-protected aminoethyl phenyl thioether ligand (eq 2). Carboxylic acids containing α -hydrogens are also compatible with this catalyst. The γ -lactone products formed by C(sp³)-H olefination and subsequent 1,4-addition can be found in many bioactive compounds (Figure 1).⁸ The hydrolytic opening of the lactones provides synthetically useful β -olefinated aliphatic acids or 1,4-dihydroxy compounds (eq 2).

Our initial investigation into carboxyl-directed β -C(sp³)-H olefination employed 2,2-dimethylbutyric acid **1b** as a model substrate and benzyl acrylate **2a** as an olefin coupling partner. We have previously established that counteranions, such as Na⁺ or K⁺, promote Pd(II) insertion into *ortho*- or β -C-H in carboxylic acid substrates by engaging K² coordination with the carboxylate.⁵ We were pleased to observe that using Pd(OAc)₂ (10 mol%) in the presence of Na₂HPO₄·7H₂O as the base and Ag₂CO₃ as the oxidant provided olefination product **3b** in 16% yield (Table 1). We next tested representative pyridine- or quinoline-based ligands (**L1**–**L4**) developed in our laboratory to exploit ligand acceleration. To our delight, the yield was improved to 57% by using the simple monodentate 2,6-lutidine ligand **L2**. Further screening of pyridone ligands (**L5**–**L7**) which were identified to enable *meta*-C(sp²)-H arylation of phenyl acetic acids^{5e} only gave inferior yields. After extensive screening of different bases and external oxidants, the product **3b** could be isolated in 70% when we used K₂HPO₄ as the base and AgOAc as the oxidant in the presence of 2,6-lutidine **L2** (15 mol%). However, use of this ligand is limited to carboxylic acids α -containing quaternary centers.

To overcome this limitation, we turned our attention to the bidentate ligands that were recently developed to accelerate C(sp³)-H activation in our laboratory. Guided by ligand-accelerated *ortho*-C(sp²)-H olefination of phenyl acetic acids^{5c} and β -C(sp³)-H arylation of α -branched carboxylic acids,^{4d, 4e} we tested mono-*N*-protected amino acid (MPAA) ligands. However, this type of ligand gave poor yields. Other bidentate ligands (**L11**–**L13**), previously found to promote enantioselective intermolecular C(sp³)-H activation,^{4a, 4b} gave moderate yield with substrate **1b**, but displayed no reactivity with α -hydrogen containing carboxylic acids. The essential role played by the NHAc group in the bidentate ligands (**L8**–**L13**) prompted us to replace the quinoline and oxazoline by sulfur as a soft σ -donor.⁹ We prepared acetyl-protected aminoethyl phenyl thioether ligand **L14** in two steps from commercial available 2-aminoethyl bromide. Ligand **L14** afforded a dramatic increase in reactivity providing a 90% yield. The product could be isolated in nearly quantitative yield (96%) by increasing the temperature and using Pd(TFA)₂. **L14**, a bench-stable and odorless solid, was easily recycled after the reaction, demonstrating its stability in the presence of a mild oxidant (Ag salt in this case). Efforts to introduce substitution on the ligand backbone (**L15**) did not enhance the reactivity. It is worth-noting that the formation of the γ -lactone *via* the intramolecular conjugate addition secured the exclusive mono-selectivity which has not been possible in other C–H functionalizations in the presence of multiple β -C–H bonds.

With the optimal ligand and reaction conditions in hand, the scope of aliphatic carboxylic acid substrates was evaluated (Table 2). For aliphatic acids bearing α -quaternary centers, both 2,6-lutidine **L2** and the thioether ligand **L14** are effective with the latter being superior (**3a**–**3h**). Various α -dialkyl substituted propionic acids were olefinated to give the desired γ -lactones in good to excellent yields (**3a**–**3d**). Phenyl groups at the β - or γ -positions of the carboxyl group were well tolerated (**3e**, **3f**, and **3m**) and remained intact despite the potentially reactive *ortho*-C(sp²)-H bonds. Substrates containing a coordinative heteroatom such as oxygen (**1g**, **1h**, **1s**, and **1x**) or nitrogen (**1p**) were also compatible with the β -C(sp³)-H olefination conditions. Gemfibrozil (**1g**), which is an oral drug used to lower lipid levels,¹⁰ was converted to the corresponding γ -lactone **3g** in 81% yield. The use of the newly developed ligand **L14** has rendered a broad range of α -hydrogen containing carboxylic acids (**1i**–**1q**) reactive under the standard conditions. These substrates are typically challenging due to the lack of a favorable Thorpe-Ingold effect as well as the interfering acidic α -C–H bond. The olefination of *N*-phthaloyl alanine substrate **1p** is particularly interesting considering the importance of α -amino lactones. This protocol was also successfully extended to the olefination of cyclopropyl and cyclobutyl C–H bonds (**3q**–**3x**), affording highly strained fused bicyclic lactones. The presence of hydroxyl (**3s**) and halogen (**3t**) groups in those lactones offers a synthetic handle for further elaboration.

We next evaluated the scope of the olefin coupling partners by using pivalic acid **1a** as the pilot acid substrate (Table 3). The olefination with various acrylate derivatives proceeded in excellent yields (**4a**–**4c**). Other electron-withdrawing groups attached to the olefins including amide (**2d**), ketone (**2e**), nitrile (**2f**), sulfone (**2g**), and phosphonate (**2h**), were all compatible with the olefination conditions, providing the desired γ -lactones in excellent yields. *N*-aryl or alkyl maleimides (**2i**–**2k**) were also found to be suitable coupling partners

under the optimized conditions, providing diverse spirocyclic pyrrolidines in moderate to excellent yields.

Coupling of an alkyl fragment with an olefin is highly valuable due to the lack of success of analogous Heck couplings. To demonstrate the synthetic utility of these C(sp³)-H olefination products, we performed the olefination of pivalic acid **1a** with benzyl acrylate **2a** on gram scale to obtain the γ -lactone **3a** in 93% isolated yield (Scheme 1). The γ -lactone was then successfully transformed into three structurally distinct synthons: (1) selective hydrolysis of the ester under the acidic conditions gave the γ -lactone **5a** which can be further elaborated to other compounds by decarboxylative coupling;¹¹ (2) hydrolysis in the presence of sodium hydroxide generated adipic acid derivative **5b** which is widely used in the polymer chemistry industry; (3) reduction of the lactone and ester afforded the 1,4,6-triol **5c**.

In conclusion, we have developed a new thioether based bidentate ligand **L14** that effectively promotes β -C(sp³)-H olefination of a broad range of free carboxylic acids. The unique synthetic utility of olefination is demonstrated by the synthesis of γ -lactones, β -vinylated acids, and γ -hydroxylated acids, which has not been possible using an auxiliary approach. This transformation provides a highly desirable synthetic disconnection considering the challenges in developing analogous Heck couplings due to premature β -hydride elimination.

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Figure 1.
Bioactive Compounds Containing γ -Lactone and Derivatives

Scheme 1. Gram-Scale Experiment and Synthetic Application

^a Conditions A: **1a** (12.0 mmol), **2a** (2.0 eq), Pd(TFA)₂ (10 mol%), **L14** (10 mol%), Na₂HPO₄·7H₂O (1.0 eq), Ag₂CO₃ (1.0 eq), HFIP, 120 °C, 12 h.

^b Conditions B: **3a** (0.2 mmol), 6N HCl, 80 °C, overnight.

^c Conditions C: **3a** (1.0 mmol), NaOH (4.0 eq), EtOH/H₂O, reflux.

^d Conditions D: **3a** (0.2 mmol), LAH (4.0 eq), THF, rt.

Table 1.

Ligand Development for β -C(sp³)-H Olefination^{a, b}

w/o ligand 16%	 L1, 16%	 L2, 57% (70% ^c)	 L3, 54%
 L4, 38%	 L5, 4%	 L6, 21%	 L7, 18%
 L8, 41%	 L9, 3%	 L10, 20%	 L11, 59%
 Ar = 3,5-(<i>t</i> -Bu) ₂ C ₆ H ₃ L12, 55%	 Ar = 3,5-(<i>t</i> -Bu) ₂ C ₆ H ₃ L13, 46%	 L14, 90% (96% ^d)	 L15, 54%

^aConditions A: **1b** (0.1 mmol), **2a** (2.0 eq), Pd(OAc)₂ (10 mol%), ligand (10 mol% for bidentate ligands (**L8-L15**) or 20 mol% for monodentate ligands (**L1-L7**)), Na₂HPO₄·7H₂O (1.0 eq), Ag₂CO₃ (1.0 eq), HFIP, 90 °C, 12 h.

^bThe yields were determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard.

^cConditions B: **1b** (0.1 mmol), **2a** (2.0 eq), Pd(OAc)₂ (10 mol%), **L2** (15 mol%), K₂HPO₄ (2.0 eq), Ag₂CO₃ (2.0 eq), HFIP, 100 °C, 24 h. Isolated yield.

^dConditions C: **1b** (0.1 mmol), **2a** (2.0 eq), Pd(TFA)₂ (10 mol%), **L14** (10 mol%), Na₂HPO₄·7H₂O (1.0 eq), Ag₂CO₃ (1.0 eq), HFIP, 120 °C, 12 h. Isolated yield.

Table 2.

Substrate Scope for β -C(sp³)-H Olefination^{a, b} ^a Conditions A: **1** (0.1 mmol), **2a** (2.0 eq), Pd(TFA)₂ (10 mol%), **L14** (10 mol%), Na₂HPO₄·7H₂O (1.0 eq), Ag₂CO₃ (1.0 eq), HFIP, 120 °C, 12 h.^b Isolated yields.

^c Conditions B: **1** (0.1 mmol), **2a** (2.0 eq), Pd(OAc)₂ (10 mol%), **L2** (15 mol%), K₂HPO₄ (2.0 eq), Ag₂CO₃ (2.0 eq), HFIP, 100 °C, 24 h.

^d Conditions C: **1p** (0.1 mmol), **2a** (2.0 eq), Pd(OAc)₂ (10 mol%), **L12** (10 mol%), CsOAc (1.0 eq), Ag₂CO₃ (1.0 eq), HFIP, 100 °C, 24 h.

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Table 3.

Olefin Scope for β -C(sp³)-H Olefination^{a, b} ^a Conditions A: **1a** (0.1 mmol), **2** (2.0 eq), Pd(TFA)₂ (10 mol%), **L14** (10 mol%), Na₂HPO₄·7H₂O (1.0 eq), Ag₂CO₃ (1.0 eq), HFIP, 120 °C, 12 h.^b Isolated yields.^c Conditions B: **1a** (0.1 mmol), **2** (2.0 eq), Pd(OAc)₂ (10 mol%), **L14** (10 mol%), Ag₂CO₃ (1.0 eq), HFIP, 120 °C, 12 h.