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Ligand-Enabled β-C(sp^3)–H Olefination of Free Carboxylic Acids

Zhe Zhuang,[†,⊥] Chang-Bin Yu,[†,⊥] Gang Chen,[†] Qing-Feng Wu,[†] Yi Hsiao,[‡] Candice L. Joe,[‡] Jennifer X. Qiao,[§] Michael A. Poss,[§] and Jin-Quan Yu[*,†]

[†]*Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, United States*

[‡]*Chemical and Synthetic Development, Bristol-Myers Squibb, 1 Squibb Drive, New Brunswick, New Jersey 08903, United States*

[§]*Discovery Chemistry, Bristol-Myers Squibb Company, PO Box 4000, Princeton, New Jersey 08543, United States*

*yu200@scripps.edu

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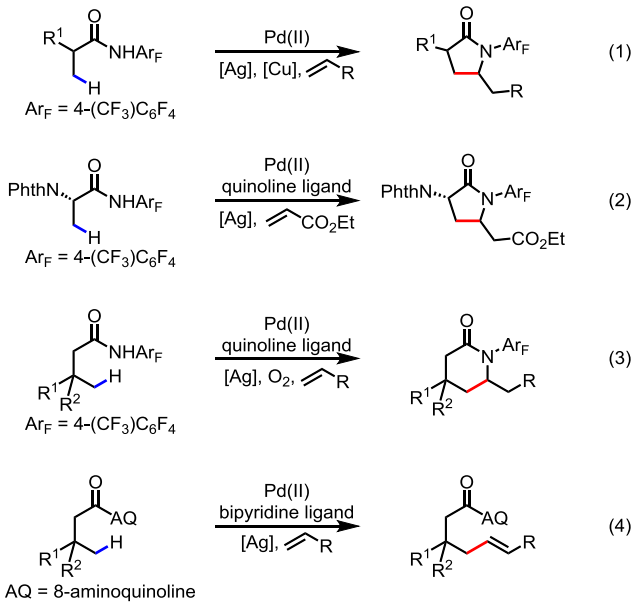
Abstract. An acetyl-protected aminoethyl phenyl thioether has been developed to promote C(sp^3)–H activation. Significant ligand enhancement is demonstrated by the realization of the first Pd(II)-catalyzed olefination of C(sp^3)–H bonds of free carboxylic acids without using an auxiliary. Subsequent 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.

1. Introduction

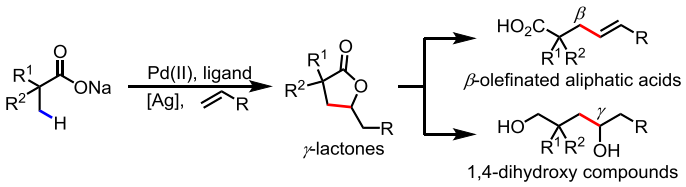
Carboxylic acids are readily available and highly versatile starting materials in organic synthesis. In the past decade, a number of directed C(sp^3)–H activation reactions of aliphatic acids using various directing groups have provided unprecedented synthetic disconnections.[1] For example, Pd-catalyzed C(sp^3)–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(sp^3)–H activation reactions are rare. K_2PtCl_4-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(sp^3)–H arylation of free carboxylic acids[3] and was further improved by ligand acceleration.[4,5] However, further development of carboxyl-directed C(sp^3)–H functionalization reactions have only been successful using exogenous auxiliaries. In particular, the development of a C(sp^3)–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 a few precedents using auxiliaries have been reported.[7] In 2010, our group has reported the first example of Pd(II)-catalyzed β-C(sp^3)–H olefination of *N*-aryl amide with acrylates (Scheme 1, eq 1).[7a] The highly electron-withdrawing perfluorinated *N*-arylamide auxiliary was crucial to effect C(sp^3)–H activation. In 2014, the reaction efficiency in β-C(sp^3)–H olefination of amide was dramatically improved by using a newly tricyclic quinoline ligand developed by our group; alanine-derived amide could be successfully olefinated (Scheme 1, eq 2).[7b] Subsequently in 2014, the combination of a quinoline-based ligand and a weakly coordinating amide directing group also allowed for γ-C(sp^3)–H olefination of amide for the first time (Scheme 1, eq 3).[7c] However, these reactions suffer from the undesired subsequent cyclization reaction with the nitrogen containing auxiliary, preventing further synthetic elaborations. Recently, the Maiti group used a bidentate directing group to achieve γ-C(sp^3)–H olefination, albeit largely limited to substrates containing quaternary carbon centers (Scheme 1, eq 4).[7f]

Scheme 1. C(sp^3)–H Olefination of Carboxylic Acid Derivatives



Herein we report the first example of β-C(sp^3)–H olefination of free carboxylic acids enabled by an acetyl-protected aminoethyl phenyl thioether ligand (Scheme 2). Carboxylic acids containing α-hydrogen are also compatible with this catalyst. The γ-lactone products formed by C(sp^3)–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 (Scheme 2).

Scheme 2. β-C(sp^3)–H Olefination of Carboxylic Acids and Subsequent Lactonization



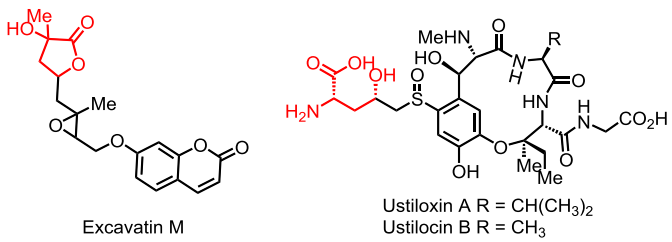


Figure 1. Bioactive Compounds Containing γ-Lactone and Derivatives

2. Results and Discussion

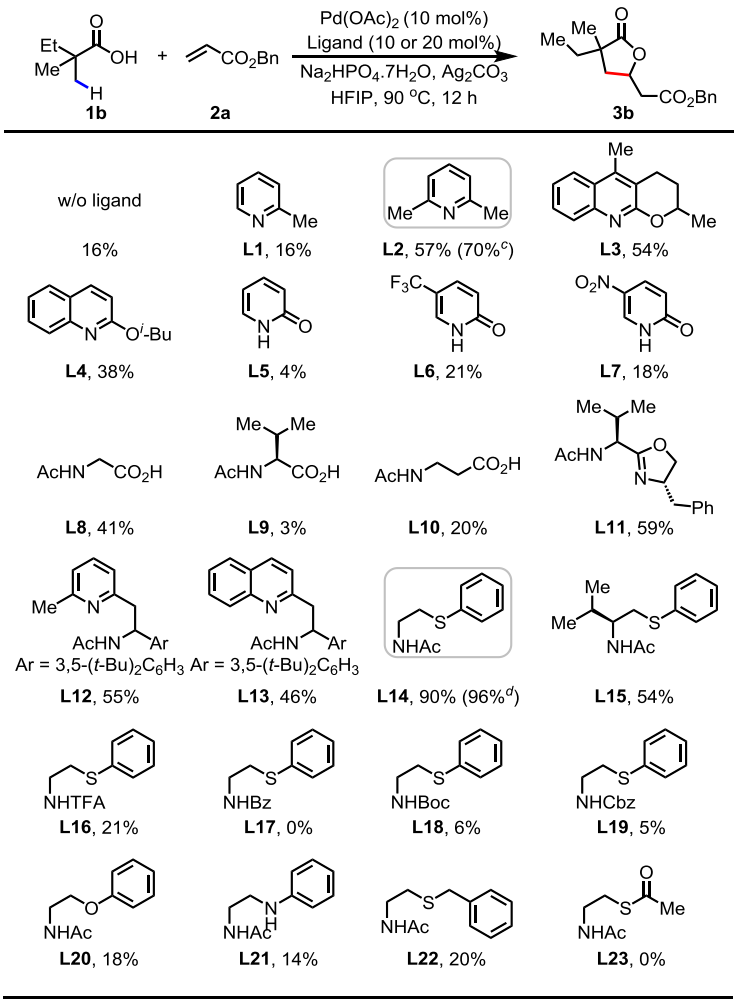
Our initial investigation into carboxyl-directed *β*-C(sp^3)–H olefination employed 2,2-dimethylbutyric acid **1b** as a model substrate and benzyl acrylate **2a** as an olefin coupling partner. We have previously established that countercations, such as Na^+ or K^+, promote Pd(II) insertion into *ortho*- or *β*-C–H in carboxylic acid substrates by engaging K^2 coordination with the carboxylate.[5] We were pleased to observe that using $Pd(OAc)_2$ (10 mol%) in the presence of $Na_2HPO_4{\cdot}7H_2O$ as the base and Ag_2CO_3 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 exploite 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(sp^2)–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 K_2HPO_4 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 containing *α*-quaternary centers.

To overcome this limitation, we turned our attention to the bidentate ligands that were recently developed to accelerate C(sp^3)–H activation in our laboratory. Guided by ligand-accelerated *ortho*-C(sp^2)–H olefination of phenyl acetic acids[5c] and *β*-C(sp^3)–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(sp^3)–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.

To investigate the impact of ligand structure on the reaction efficiency, systematic ligand modification on **L14** have been conducted. The protecting group of the amino group has noticeable influence on the reactivity: Changing Ac to TFA (**L16**), Bz (**L17**), Boc (**L18**), or Cbz (**L19**) decreased the yield considerably, which revealed that the NHAc might be involved in the C(sp^3)–H cleavage step. Replacing the sulfur atom with σ-donor oxygen (**L20**) or nitrogen (**L21**) led to the loss of reactivity. Alkyl protected (**L22**) or Ac protected (**L23**) thio-ligands also proved inactive indicating the importance of PhS moiety. The rate profile of the ligand **L14** with substrate **1b** (see Supporting Information) also indicated the dual role of thioether ligand in the olefination: (1) the initial rate of the reaction is accelerated by a factor of twenty; (2) Pd catalyst is more stable over reaction time affording higher turnover numbers.

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

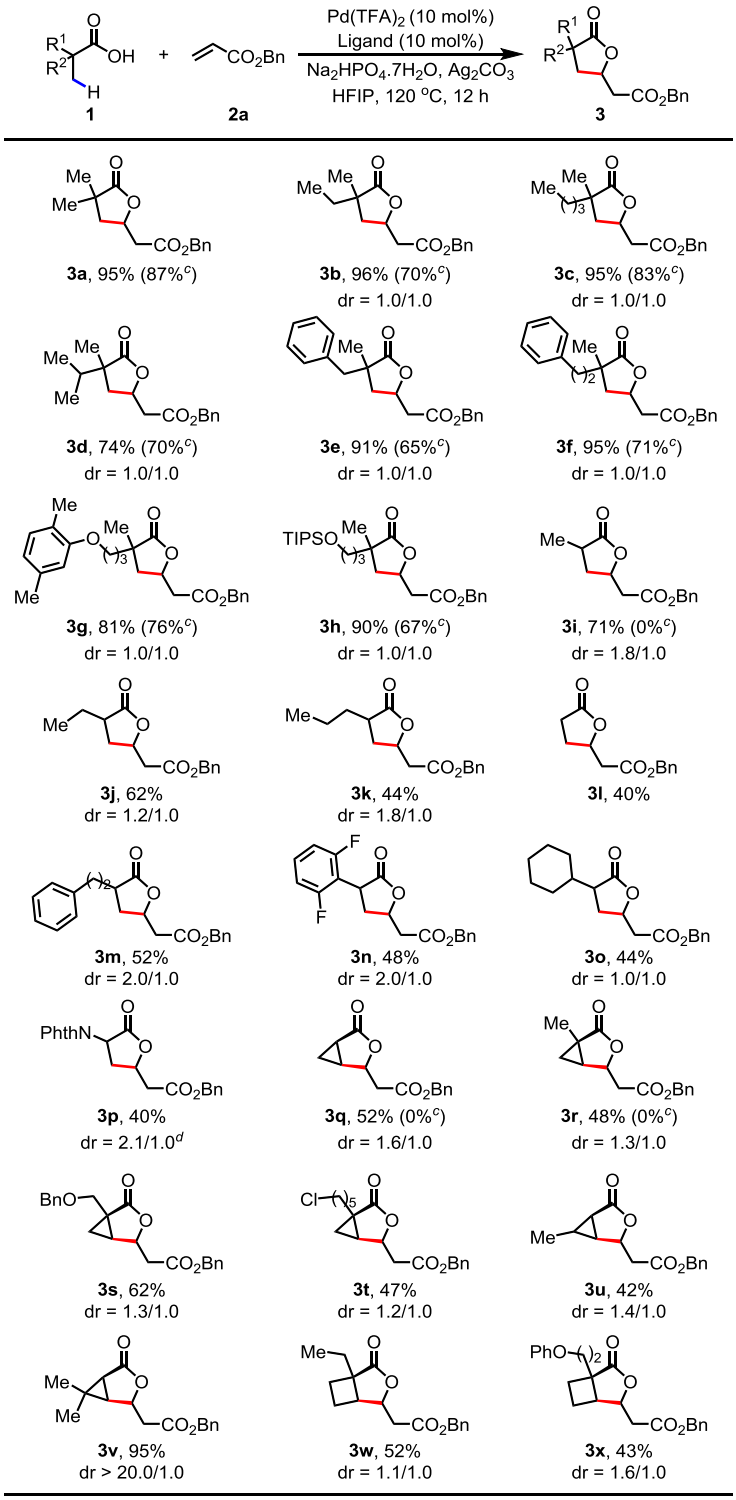


[a]Conditions A: **1b** (0.1 mmol), **2a** (2.0 eq), $Pd(OAc)_2$ (10 mol%), ligand (10 mol% for bidentate ligands (**L8**–**L23**) or 20 mol% for monodentate ligands (**L1**–**L7**)), $Na_2HPO_4{\cdot}7H_2O$ (1.0 eq), Ag_2CO_3 (1.0 eq), HFIP (1.0 mL), 90 °C, 12 h. [b]The yields were determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c]Conditions B: **1b** (0.1 mmol), **2a** (2.0 eq), $Pd(OAc)_2$ (10 mol%), **L2** (15 mol%), K_2HPO_4 (2.0 eq), AgOAc (2.0 eq), HFIP (1.0 mL), 100 °C, 24 h. Isolated yield. [d]Conditions C: **1b** (0.1 mmol), **2a** (2.0 eq), $Pd(TFA)_2$ (10 mol%), **L14** (10 mol%), $Na_2HPO_4{\cdot}7H_2O$ (1.0 eq), Ag_2CO_3 (1.0 eq), HFIP (1.0 mL), 120 °C, 12 h. Isolated yield.

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(sp^2)–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(sp^3)–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.

Table 2. Substrate Scope for *β*-C(sp3)–H Olefination[a,b]

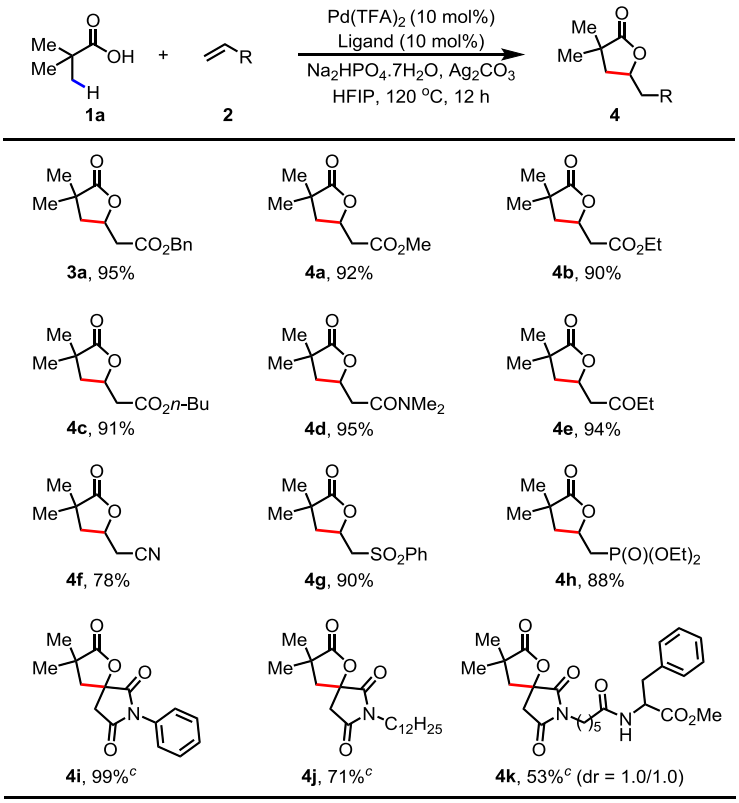


[a]Conditions A: **1** (0.1 mmol), **2a** (2.0 eq), $Pd(TFA)_2$ (10 mol%), **L14** (10 mol%), $Na_2HPO_4 \cdot 7H_2O$ (1.0 eq), Ag_2CO_3 (1.0 eq), HFIP (1.0 mL), 120 °C, 12 h. [b]Isolated yields. [c]Conditions B: **1** (0.1 mmol), **2a** (2.0 eq), $Pd(OAc)_2$ (10 mol%), **L2**

(15 mol%), K_2HPO_4 (2.0 eq), Ag_2CO_3 (2.0 eq), HFIP (1.0 mL), 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), Ag_2CO_3 (1.0 eq), HFIP (1.0 mL), 100 °C, 24 h.

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.

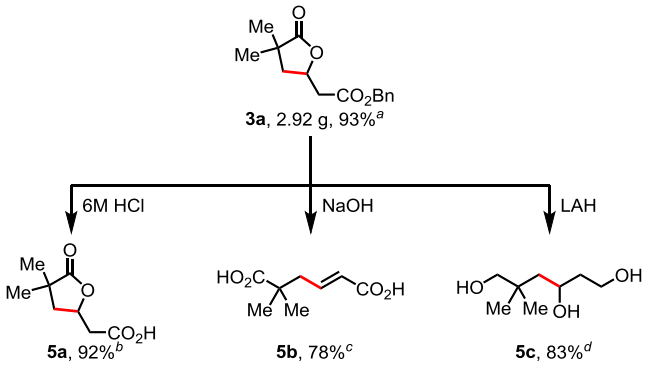
Table 3. Olefin Scope for *β*-C(sp3)–H Olefination[a,b]



[a]Conditions A: **1a** (0.1 mmol), **2** (2.0 eq), $Pd(TFA)_2$ (10 mol%), **L14** (10 mol%), $Na_2HPO_4 \cdot 7H_2O$ (1.0 eq), Ag_2CO_3 (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%), Ag_2CO_3 (1.0 eq), HFIP, 120 °C, 12 h.

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(sp^3)–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 3). 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**.

Scheme 3. Gram-Scale Experiment and Synthetic Applications



[a]Conditions A: **1a** (12.0 mmol), **2a** (2.0 eq), $Pd(TFA)_2$ (10 mol%), **L14** (10 mol%), $Na_2HPO_4.7H_2O$ (1.0 eq), Ag_2CO_3 (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/H_2O, reflux. [d]Conditions D: **3a** (0.2 mmol), LAH (4.0 eq), THF, rt.

3. Conclusion

In conclusion, we have developed a new thioether based bidentate ligand **L14** that effectively promotes β-C(sp^3)–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.

4. Experimental Section

General procedure for β-C(sp^3)–H olefination. In the control tube, $Pd(TFA)_2$ (10 mol%), ligand **L14** (10 mol%), $Na_2HPO_4.7H_2O$ (1.0 eq), Ag_2CO_3 (1.0 eq), 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) and olefin **2** (2.0 eq) were added. The reaction mixture was stirred at rt for 10 min, and then heated to 120 ^oC for 12 h (300 rpm). After being allowed to cool to room temperature, the mixture was diluted with DCM, and filtered through a pad of celite. The filtrate was concentrated *in vacuo*, and the resulting mixture purified by column chromatography or pTLC using hexane/EA (2/1) as the eluent to afford desired products. Full experimental details and characterization of new compounds can be found in the Supporting Information.

Corresponding author. *yu200@scripps.edu

Author Contributions. $^{\perp}$Z.Z. and C.-B.Y. contributed equally to this work.

Notes. The authors declare no competing financial interest.

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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.

References

1. (a) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (b) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (c) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (d) Zhu, R.-Y.; He, J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 13194. (e) Tran,

L. D.; Daugulis, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 5188. (f) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. (g) Zhu, R.-Y.; Tanaka, K.; Li, G.-C.; He, J.; Fu, H.-Y.; Li, S.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 7067. (h) Zhang, Q.; Yin, X.-S.; Chen, K.; Zhang, S.-Q.; Shi, B.-F. *J. Am. Chem. Soc.* **2015**, *137*, 8219.

2. (a) Kao, L.-C.; Sen, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1242. (b) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149.

3. Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunder, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.

4. (a) Chen, G.; Gong, W.; Zhuang, Z.; Andra, M. S.; Chen, Y.-Q.; Hong, X.; Yang, Y.-F.; Liu, T.; Houk, K. N.; Yu, J.-Q. *Science* **2016**, *353*, 1023. (b) Wu, Q.-F.; Shen, P.-X.; He, J.; Wang, X.-B.; Zhang, F.; Shao, Q.; Zhu, R.-Y.; Mapelli, C.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. *Science* **2017**, *355*, 499. (c) Chen, G.; Zhuang, Z.; Li, G.-C.; Saint-Denis, T. G.; Hsiao, Y.; Joe, C. L.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 1506. (d) Zhu, Y.; Chen, X.; Yuan, C.; Li, G.; Zhang, J.; Zhao, Y. *Nat. Commun.* **2017**, *8*, 14904. (e) Ghosh, K. K.; van Gemmeren, M. *Chem. -Eur. J.* **2017**, *23*, 17697.

5. For COONa or COOK directed diverse C(sp^2)–H activation reactions, see: (a) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 5215. (b) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. (c) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (d) Cheng, G.; Li, T.-J.; Yu, J.-Q *J. Am. Chem. Soc.* **2015**, *137*, 10950. (e) Li, G.-C.; Wang, P.; Farmer, M. E.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 6874. For Fe-catlayzed *ortho*-methylation: (f) Shang, R.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2016**, *138*, 10132.

6. For examples of intermolecular Heck-type coupling of alkyl halides and alkenes, see: (a) McMahon, C. M.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5974. (b) Zou, Y.; Zhou, J. S. *Chem. Commun.* **2014**, *50*, 3725. (c) Wang, G.-Z.; Shang, R.; Cheng, W.-M.; Fu, Y. *J. Am. Chem. Soc.* **2017**, *139*, 18307. (d) Kurandina, D.; Parasram, M.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2017**, *56*, 14212. (e) Kurandina, D.; Rivas, M.; Radzhabov, M.; Gevorgyan, V. *Org. Lett.*

2018, *20*, 357. For examples of intramolecular Heck-type coupling of alkyl halides and alkenes, see: (f) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340.

7. (a) Wasa, M.; Engle, K. M.; Yu, J-.Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680. (b) He, J; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science **2014**, 343, 1216. (*c) Li, S.; Chen, G.; Feng, C.-G.; Gong, W.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 5267. (d) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. *J. Am. Chem. Soc*. **2011**, *133*, 6541. (e) Jiang, H.; He, J.; Liu, T.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 2055. (f) Thrimurtulu, N.; Khan, S.; Maity, S.; Volla, C. M. R.; Maiti, D. *Chem. Commun.* **2017**, *53*, 12457.

8. (a) Ito, C.; Itoigawa, M.; Katsuno, S.; Omura, M.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2000**, *63*, 1218. (b) Koiso, Y.; Natori, M.; Iwasaki, S. *Tetrahedron Lett.* **1992**, *33*, 4157.

9. For allylic acetoxylation using sulfoxide ligands, see: (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. For C–H olefination of electron-rich arenes using simple thioether ligands, see: (b) Gorsline, B. J.; Wang, L.; Ren, P.; Carrow, B. P. *J. Am. Chem. Soc.* **2017**, *139*, 9605. For an early example of aminothioether ligands for allylic alkylation, see: (c) Anderson, J. C.; James, D. S.; Mathias, J. P. *Tetrahedron: Asymmetry* **1998**, *9*, 753. For an early example of thio-based chiral ligands for Ru-catalyzed asymmetric hydrogenation, see: (d) Zaitsev, A. B.; Adolfsson, H. *Org. Lett.* **2006**, *8*, 5129.

10. Pueyo Palazón, C.; Alfón, J.; Gaffney, P.; Berrozpe, M.; Royo, T.; Badimon, L. *Atherosclerosis* **1998**, *136*, 333.

11. (a) Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 2174. (b) Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S. *Science* **2016**, *352*, 801.

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