Published in final edited form as:

Nat Chem. 2019 June ; 11(6): 571–577. doi:10.1038/s41557-019-0245-6.

Reversing Conventional Site-Selectivity in C(sp³)–H Bond Activation

Guoqin Xia¹, Jiang Weng¹, Luoyan Liu¹, Pritha Verma¹, Ziqi Li¹, and Jin-Quan Yu¹

¹Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road. La Jolla, California 92037, USA.

Abstract

One of the core challenges in developing C–H activation reactions is to distinguish multiple C–H bonds that are nearly identical in terms of electronic properties and bond strengths. Through recognition of distance and molecular geometry, remote C(sp²)–H bonds have been selectively activated in the presence of proximate ones^{1–2}. Yet achieving such unconventional site selectivity with C(sp³)–H bonds remains a paramount challenge. Here we report a combination of a simple pyruvic acid derived directing group and a 2-pyridione ligand that enables the preferential activation of the distal γ -C(sp³)–H bond over the proximate β -C(sp³)–H bonds for a wide range of alcohol derived substrates. Competition experiment of five- and six-membered cyclopalladation step as well as kinetic experiments demonstrate the feasibility of using geometric strain to reverse the conventional site selectivity in C(sp³)–H activation.

Developing C–H activation reactions as new retrosynthetic disconnections could offer a multitude of novel synthetic strategies due to the abundance of positionally diverse C–H bonds^{3–4}. On the other hand, the great resemblance between these C–H bonds in terms of bond strength and electronic properties presents a tremendous challenge for achieving regioselectivity. This difficulty escalates with metalation chemistry because in such processes, the numerous primary or secondary C–H bonds are nearly indistinguishable by the metal. For example, despite the recent advances in developing a wide range of Pd-catalyzed C(sp³)–H activation reactions, their regioselectivity is largely restricted to the cleavage of the C–H bond that will result in five-membered cyclopalladation^{5–12}. Therefore, it is fundamentally important to develop strategies to switch the selectivity of the key metalation step from five-membered to six-membered cyclopalladation (Fig. 1b). Such

Reprints and permissions information is available at www.nature.com/reprints.

Correspondence and requests for materials should be addressed to J.-Q. Y. (yu200@scripps.edu).

Author Contributions J.-Q. Y. and G. X. conceived the concept. G. X. developed the distal C(sp³)–H arylation for aliphatic alcohols. G. X. and J. W. made the alcohol substrates and investigated the scope. G. X., Z. L. and L. L. conducted the experiments for aryl iodide scope. J.-Q. Y. supervised the project.

The authors declare no competing financial interests.

Readers are welcome to comment on the online version of this article.

Data Availability

The data supporting the findings of this study are available within the article and its Supplementary Information files. Metrical parameters for the structure of **6** (see Supplementary Information) are available free of charge from the Cambridge Crystallographic Data Centre (<https://www.ccdc.cam.ac.uk/>) under reference number CCDC-1872396.

Supplementary Information is available in the online version of the paper.

strategies will allow palladium catalysts to preferentially functionalize widespread carbon centers that are one bond further away from existing functional groups.

Five-membered cyclopalladation of $C(sp^3)-H$ bonds has been known to be both kinetically and thermodynamically more favored over the six-membered or larger sized counterparts since its discovery in 1970s (Figure 1a)^{13–16}. As a consequence, distal $C(sp^3)-H$ functionalization through a six-membered palladacycle is limited to the following rare examples: a) when five-membered cyclopalladation is not possible due to the lack of primary or secondary $C-H$ bonds at the appropriate carbon^{17–21}; b) the five-membered palladacycle intermediate generated from a strong coordinating bidentate directing group is too stable to react with a special functionalization reagent, namely, 1,2-diphenyl alkynes²². In addition, this single observation is only limited to more reactive methyl $C-H$ bonds. Notably, Ir-catalyzed intramolecular silylation using a tethered silyl hydride as the directing group proceeds through a six-membered cycloiridation. However, this selectivity is dictated by the subsequent cyclization to afford the five-membered oxasilolane because the four-membered oxasilolane formation from the five-membered cycloiridation is disfavored^{23–24}. In this context, intermolecular $\gamma-C-H$ activation of alcohol substrates is especially challenging as the hydroxyl directed six-membered cyclopalladation of $C(sp^3)-H$ bonds has not been demonstrated thus far^{25–26}. The design of directing groups for $C(sp^3)-H$ functionalization of alcohols has been reported^{27–28}, albeit limited to $\beta-C-H$ bonds and oxidation.

Here we report the realization of $\gamma-C(sp^3)-H$ arylation of aliphatic alcohols via six-membered cyclopalladation by a designed pyruvic acid derived directing group in combination with a 2-pyridone ligand. The rationale of our directing group design is based upon the ring strain of the bicyclic palladacycles. While previous bidentate directing groups also involve bicyclic palladacycles, the key to our design is to incorporate multiple double bonds into the bicyclic palladacycles so that the 5,5-fused ring is more strained than the 5,6-fused ring, and thus favors the six-membered cyclopalladation. It is well-known that multiple sp^2 centers on a small ring will increase the ring strain²⁹ (Figure 1c). Importantly, γ -selectivity for both primary and methylene $C-H$ bonds is achieved on acyclic and cyclic alcohols in the presence of $\beta-C-H$ bonds (Figure 1d).

We selected alcohol substrates to search for a practical directing group and catalyst system that can reverse the commonly favored β -selectivity to γ -selectivity because: a) alcohols are abundant and synthetically versatile starting materials³⁰; b) $\gamma-C-H$ activation of alcohols using Pd insertion has not been reported to date. The first challenge is to realize the palladation of $\gamma-C-H$ bonds of alcohol substrates. A simple pyruvic acid directing group (**DG1**) was attached to isobutyl alcohol containing no β -primary or β -methylene $C-H$ bonds for exploratory investigations. This directing group can be installed via two steps in one pot, and simply purified by basic and acidic work up without column. However, no arylation product was observed under various conditions. Through extensive ligand screening we discovered that electron-deficient 2-pyridone, previously found to be beneficial for both $C(sp^2)-H$ and $C(sp^3)-H$ functionalization^{21, 31}, was crucial for the $C(sp^3)-H$ arylation of aliphatic alcohol when using **DG1** as the directing group, arylation product **2a** and **2a'** were obtained in 75% isolated yield (mono: di = 2.3:1) (Figure 2a). Electron-deficient 2-pyridones

not only stabilize the palladium catalyst but also lower the transition-state energy of C-H cleavage step³¹. To examine the robustness of this γ -C-H arylation protocol, we subjected a series of alcohol substrates bearing no β -primary or β -methylene C(sp³)-H bonds to the standard conditions. We found that methyl groups in primary alcohols with substitution at the β -position were arylated smoothly to give the desired products in good to excellent yields (**2a-2g**). Secondary alcohols are also reactive, affording the arylation products in good yields (**2h** and **2h'**). Interestingly, the naturally occurring enantiopure (1R)-endo-(+)-fenchol was arylated specifically at the C9 position in 84% yield (**2i**). The efficiency of this protocol was further showcased by arylation of γ -methylene C-H bonds in both acyclic and cyclic alcohols (**2j-2l**). A wide range of aryl iodides were also compatible, affording the desired γ -arylation product in good yields. For example, a series of meta-substituted electrophiles, including electron-donating (**3a-3c**) and electron-withdrawing groups (**3d-3h**), gave the products in good to excellent yields; halides were also compatible providing the arylation products in good yields (**3i, 3j**). A series of para-substituted aryl iodides also afforded the products in good to excellent yields (**3k-3t**). Ortho-substituted aryl iodides were not reactive enough under current conditions, except for 2-fluorophenyl iodide (**3u**); poly-substituted aryl iodides provided the arylation product in good yields (**3v, 3w**). 5-iodoindole was also a compatible substrate, providing the product in 62% yield (**3x**).

With this effective protocol for γ -C-H arylation in hand, we began to address a fundamental challenge, namely, achieving distal selectivity in C(sp³)-H activation by favoring six-membered cyclopalladation over the five-membered process. Such a switch of regioselectivity could double the utility of current C(sp³)-H activation reactions based on five-membered cyclopalladation by enabling the functionalization of many previously inaccessible C-H bonds. Notably, most of the alcohol substrates contain both β - and γ -primary and methylene C-H bonds. Considering that primary C-H bonds are more reactive than methylene C-H bonds, 3-pentanol containing β -methylene C-H bonds was chosen for initial investigation. Arylation products were obtained in 84% isolated yield ($\gamma/\beta = 2:1$) when using **DG1** as the directing group. Through further tuning of the directing group (see supplementary information), we found that the amide directing group derived from 2,3,5,6-tetrafluoro-4-CF₃-phenyl amine (**DG2**) afforded the γ -C(sp³)-H bond arylation exclusively in 72% yield (**5b** and **5b'**). Thus, we have developed two protocols for γ -C-H activation of alcohols: **DG1** with pyridone ligand displayed higher reactivity but lower selectivity ($\gamma/\beta = 2:1$); **DG2** alone afforded lower yields but with exclusive γ -selectivity. These two designed L, X-type directing groups, utilized in conjunction with electron-deficient pyridone ligands, are uniquely capable of enabling the γ -C-H arylation, as a wide range of other directing groups and ligands, and combination of thereof, are ineffective (see supplementary information). Remarkably, even though the β -primary C-H bonds are typically far more reactive than the γ -primary C-H bonds ($>20:1$)²⁷⁻²⁸, a complete reversal in site selectivity in cyclometalation was realized using our protocol (**5e-5g**). Highly γ -selective arylation of alcohol substrates **4a-4d** shows the generality of the reversal of regioselectivity.

The selective activation of γ -methylene C-H bonds over β -methylene C-H bonds is far more challenging: 1) γ -methylene C-H activation via metalation has not been reported to date; 2) steric demand for γ -methylene C-H bond and β -methylene C-H bond metalation

are similar. Surprisingly, substrate derived from 4-heptanol containing four β - and four γ -methylene C–H bonds afforded exclusive γ -selectivity in 45% yield (**5h**), other similar substrates also afforded the γ -selectivity exclusively (**5i**, **5j**). This reversal of site selectivity was also achieved with cyclic alcohol substrates (**5m**, **5n**). Unsurprisingly, γ -C–H arylation is less favored with smaller rings due to the rigid geometric strain. While both β - and γ -arylated products were obtained with cyclopentanol substrate affording a ratio of 2:1 in favor of β -arylation (**5l**), cyclobutanol substrate afforded β -arylation product in 93% yield due to the extreme geometric strain (**5k**). Finally, γ -arylation is also preferred over β -arylation with primary alcohol substrates (**5o**, **5p**), albeit in lower selectivity (γ : β = 3:1). This result, although remains to be fully optimized, also showcases the generality of using geometric strain to reverse site selectivity.

To gain further insight into the origin of this unconventional γ -selectivity, we performed the deuterium incorporation experiment under the reaction conditions in the presence of ArI. Lack of D-incorporation suggests that the arylation step is sufficiently fast to outcompete the reversibility of the C–H activation step (Figure 4a). KIE experiments showed that the C–H cleavage step was the rate-determining step for both β - and γ -C–H arylation (KIE_γ = 4.4, KIE_β = 2.7, Figure 4b). In addition, the kinetic experiments show that the initial rate of γ -C(sp³)–H arylation is faster than β -C(sp³)–H bond (k_γ/k_β = 4.1, Figure 4b), which is consistent with the product distribution. These combined results provide evidence that the site selectivity originates from the C–H cleavage step, rather than the subsequent oxidative addition of palladacycle with the aryl iodide. To directly compare the cyclopalladation of β - and γ -C–H bonds, substrates **1g** and **7** were subjected to cyclopalladation conditions in a 1:1 ratio. Only 6-membered palladacycle **6** was isolated in 62% yield; this structure was characterized by X-ray diffraction. By contrast, 5-membered palladacycle **8** was not observed. The palladacycle **6** was able to react with aryl iodide to yield product **2g** under the established conditions (Figure 4c). Finally, we found the methyl ester of the directing group **DG1** can be easily removed under Pd/C hydrogenation conditions with almost quantitative yield, and **DG2** can be removed efficiently using copper powder as the reductant (Figure 4d).

In conclusion, we have developed a new protocol for functionalization of distal C(sp³)–H bonds of aliphatic alcohols. In this context, conventionally favored 5-membered cyclopalladation was reversed to 6-membered cyclopalladation by introducing a geometrically strained directing group. This new protocol works with a wide range of substrates and tolerates a series of functional groups. A simple procedure for both installation and removal of the directing group renders this protocol highly practical. The strategy disclosed herein to favor six-membered over five-membered cyclopalladation may serve as a general principle for achieving the distal C(sp³)–H functionalization of other synthetically or medically useful compounds.

Methods Summary

General procedure for γ -selective C(sp³)-H activation of aliphatic alcohol.

To a 10-mL reaction vial with a magnetic stir bar was added **DG1**-tethered alcohol substrate (0.1 mmol), aryl iodide (0.3 mmol), palladium acetate (0.01 mmol), 3-nitro-5-chloro-pyridone (0.04 mmol) and silver trifluoroacetate (0.25 mmol), the mixture was dissolved with 1 mL of HFIP and then the vial was capped. The reaction mixture was stirred at 100 °C for 20 hours. After cooling to room temperature, the mixture was diluted with 2 mL of ethyl acetate and filtered through a pad of Celite, then washed with another 2 mL of ethyl acetate. The filtrate was concentrated and re-dissolved with 5 mL of methanol, cooled with an ice-bath, sulfonyl chloride (0.2 mL) was added slowly. The resulting mixture was stirred at room temperature for 30 min, then concentrated, the residue was purified by preparative thin-layer chromatography to get the arylation product. Full experimental details and characterization of compounds are given in Supplementary Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We gratefully acknowledge The Scripps Research Institute, the NIH (National Institute of General Medical Sciences grant 2R01GM084019) for their financial support.

References

1. Leow D, Li G, Mei T-S, Yu J-Q Activation of remote meta-C-H bond assisted by an end-on template. *Nature* 486, 518–522 (2012). [PubMed: 22739317]
2. Zhang Z, Tanaka K, Yu J-Q Remote site-selective C-H activation directed by a catalytic bifunctional template. *Nature* 543, 538–542 (2017). [PubMed: 28273068]
3. Gutekunst WR, Baran PS C–H functionalization logic in total synthesis. *Chem. Soc. Rev* 40, 1976–1991 (2011). [PubMed: 21298176]
4. McMurray L, O'Hara F, Gaunt MJ Recent developments in natural product synthesis using metal-catalysed C–H bond functionalisation. *Chem. Soc. Rev* 40, 1885–1898 (2011). [PubMed: 21390391]
5. Lyons TW, Sanford MS Palladium-catalyzed ligand-directed C-H functionalization reactions. *Chem. Rev* 110, 1147–1169 (2010). [PubMed: 20078038]
6. Ackermann L Carboxylate-assisted transition-metal-catalyzed C-H bond functionalizations: mechanism and scope. *Chem. Rev* 111, 1315–1345 (2011). [PubMed: 21391562]
7. Daugulis O, Roane J, Tran LD Bidentate, monoanionic auxiliary-directed functionalization of carbon-hydrogen bonds. *Acc. Chem. Res* 48, 1053–1064 (2015). [PubMed: 25756616]
8. Gensch T, Hopkinson MN, Glorius F, Wencel-Delord J Mild metal-catalyzed C–H activation: examples and concepts. *Chem. Soc. Rev* 45, 2900–2936 (2016). [PubMed: 27072661]
9. Baudoin O Ring construction by palladium(0)-catalyzed C(sp³)-H activation. *Acc. Chem. Res* 50, 1114–1123 (2017). [PubMed: 28375627]
10. Newton CG, Wang S-G, Oliveira CC, Cramer N Catalytic enantioselective transformations involving C-H bond cleavage by transition-metal complexes. *Chem. Rev* 117, 8908–8976 (2017). [PubMed: 28212007]
11. He J, Wasa M, Chan KSL, Shao Q, Yu J-Q Palladium-catalyzed transformations of alkyl C–H bonds. *Chem. Rev* 117, 8754–8786 (2017). [PubMed: 28697604]

12. Ano Y, Tobisu M, Chatani N Palladium-catalyzed direct ethynylation of C(sp³)-H bonds in aliphatic carboxylic acid derivatives. *J. Am. Chem. Soc* 133, 12984–12986 (2011). [PubMed: 21790123]
13. Cheney AJ, Shaw BL Transition metal–carbon bonds. Part XXXI. Internal metallations of palladium(II)-t-butyl-di-o-tolylphosphine and di-t-butyl-o-tolylphosphine complexes. *J. Chem. Soc., Dalton Trans* 0, 860–865 (1972).
14. Constable AG, McDonald WS, Sawkins LC, Shaw BL Palladation of dimethylhydrazones, oximes, and oxime O-allyl ethers: crystal structure of [Pd3(ON = C_iPrPh)₆]. *J. Chem. Soc., Chem. Commun* 1061–1062 (1978).
15. Hiraki K, Fuchita Y, Matsumoto Y Doubly-chelated cyclopalladated complexes of 1,3-bis(2-pyridyl)propane. *Chem. Lett* 13, 1947–1948 (1984).
16. Balavoine G, Clinet JC Cyclopalladated 2-t-butyl-4,4-dimethyl-2-oxazoline: its preparation and use in the functionalisation of a non-activated carbon-hydrogen bond. *J. Organomet. Chem* 390, c84–c88 (1990).
17. Fuchita Y, Hiraki K, Uchiyama T Metallation of aliphatic carbon atoms. Part 1. synthesis and characterization of the cyclopalladated complexes of 2-neopentylpyridine. *J. Chem. Soc., Dalton Trans* 897–899 (1983).
18. Nadres ET, Daugulis O Heterocycle synthesis via direct C-H/N-H coupling. *J. Am. Chem. Soc* 134, 7–10 (2012). [PubMed: 22206416]
19. Reddy BVS, Reddy LR, Corey EJ Novel acetoxylation and C-C coupling reactions at unactivated positions in α -amino acid derivatives. *Org. Lett* 8, 3391–3394 (2006). [PubMed: 16836413]
20. Li S, Chen G, Feng C-G, Gong W, Yu J-Q Ligand-enabled gamma-C–H olefination and carbonylation: construction of beta-quaternary carbon centers. *J. Am. Chem. Soc* 136, 5267–5270 (2014). [PubMed: 24666182]
21. Zhu R-Y, Li Z-Q, Park HS, Senanayake CH, Yu J-Q Ligand-enabled gamma-C(sp³)-H activation of ketones. *J. Am. Chem. Soc* 140, 3564–3568 (2018). [PubMed: 29481072]
22. Xu J-W, Zhang Z-Z, Rao W-H, Shi B-F Site-selective alkenylation of δ -C(sp³)-H bonds with alkynes via a six-membered palladacycle. *J. Am. Chem. Soc* 138, 10750–10753 (2016). [PubMed: 27529372]
23. Simmons EM, Hartwig JF Catalytic functionalization of unactivated primary C–H bonds directed by an alcohol. *Nature* 483, 70–73 (2012). [PubMed: 22382981]
24. Li B, Driess M, Hartwig JF Iridium-catalyzed regioselective silylation of secondary alkyl C-H bonds for the synthesis of 1,3-diols. *J. Am. Chem. Soc* 136, 6586–6589 (2014). [PubMed: 24734777]
25. Lu Y, Wang D-H, Engle KM, Yu J-Q Pd(II)-catalyzed hydroxyl-directed C–H olefination enabled by mono-protected amino acid ligands. *J. Am. Chem. Soc* 132, 5916–5921 (2010). [PubMed: 20359184]
26. Wang X, Lu Y, Dai H-X, Yu J-Q Pd(II)-catalyzed hydroxyl-directed C–H activation/C–O cyclization: expedient construction of dihydrobenzofurans. *J. Am. Chem. Soc* 132, 12203–12205 (2010). [PubMed: 20715820]
27. Ren Z, Mo F, Dong G Catalytic functionalization of unactivated sp³ C–H bonds via exo-directing groups: synthesis of chemically differentiated 1,2-diols. *J. Am. Chem. Soc* 134, 16991–16994 (2012). [PubMed: 23030547]
28. Xu Y, Yan G, Ren Z, Dong G Diverse sp³ C-H functionalization through alcohol β -sulfonyloxylation. *Nature Chem* 7, 829–834 (2015). [PubMed: 26391083]
29. Anslyn Eric V., Dougherty Dennis A. *Modern Physical Organic Chemistry* (Sausalito, CA: University Science, 2006)
30. Falbe J, Bahrmann H, Lipps W, Mayer D, Frey GD Ullmann's Encyclopedia of Industrial Chemistry (Wiley-VCH, Weinheim, Germany, 2000)
31. Wang P, Verma P, Xia G, Shi J, Qiao JX, Tao S, Cheng PTW, Poss MA, Farmer ME, Yeung K-S, Yu J-Q Ligand-accelerated non-directed C–H functionalization of arenes. *Nature* 551, 489–494 (2017). [PubMed: 29168802]

a. Uniformly favored 5-membered cyclopalladation since 1970s **b. A significant challenge: Switching 5-membered to 6-membered cyclopalladation** **c. Design of directing group based on geometric strain** **d. Reversal of site-selectivity with representative substrates** **Figure 1. Reversing the site-selectivity for C(sp³)-H activation of aliphatic alcohol.**

a. Uniformly favored 5-membered cyclopalladation since 1970s. **b.** A significant challenge: Switching 5-membered to 6-membered cyclopalladation. **c.** Design of directing group based on geometric strain. **d.** Reversal of site-selectivity with representative substrates.

Figure 2. γ -Arylation of aliphatic alcohols.

The products were isolated after esterification of the directing group. Diastereomeric ratio was determined by ^1H NMR spectroscopy of the crude mixture. **a**, Substrates containing no β -primary or β -methylene C-H bonds. **b**, Aryl iodide scope.

Figure 3. Alcohols containing β-primary or methylene C–H bonds.

Ar^F, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl. The products for **DG1** tethered substrates were isolated after esterification of the directing group. Diastereomeric values were determined by ¹H NMR spectroscopy of the crude mixture.

Figure 4. Mechanistic study and removal of directing group.
a, Deuterium incorporation experiment. Ar = *p*-MeO₂C-C₆H₄I. **b,** KIE experiment. **c,** Synthesis and characterization of palladacycles. **d,** Removal of the directing group.