Reversing conventional site-selectivity in C(sp^3)–H bond activation

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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(sp^2)–H bonds have been selectively activated in the presence of proximate ones. Yet achieving such unconventional site selectivity with C(sp^3)–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(sp^3)–H bond over the proximate β-C(sp^3)–H bonds for a wide range of alcohol derived substrates. Competition experiment isolation of an intermediate from distal γ-C–H metalation and computational studies demonstrate the feasibility of using geometric strain to reverse the conventional site selectivity in C(sp^3)–H activation.

One Sentence Summary: Distal C(sp^3)–H bonds of aliphatic alcohols are preferentially activated over proximate C(sp^3)–H bonds through a combination of directing group design and ligand acceleration.

Main Text: 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 (*1*, *2*). 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(sp^3)–H activation reactions, their regioselectivity is largely restricted to the cleavage of the C–H bond that will result in five-membered cyclopalladation (*3-10*). 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 unconventional site selectivity will allow Pd-catalyzed C–H activation reactions to functionalize many carbon centers that are only accessible via radical (*11*, *12*) and nitrene (*13*) approaches previously.

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 (Fig. 1A) (*14-17*). 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 (*18-22*); 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 alkynes (*23*). However, this approach has not been demonstrated with methylene C–H bonds. Notably, Ir-catalyzed intramolecular silylation using a tethered silyl hydride as the directing group proceeds through a six-membered cycloiridation, with selectivity dictated by the subsequent cyclization to afford the five-membered oxasilolane (*24*, *25*). In this context, intermolecular γ-C–H activation of alcohol substrates is especially challenging as the hydroxyl directed five-membered cyclopalladation of C(sp^3)–H bonds has not been demonstrated thus far (*26*, *27*). The design of directing groups for

C(sp^3)–H functionalization of alcohols has been reported (*28*, *29*), albeit limited to β-C–H bonds and oxidation.

Here we report the realization of γ-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 (Fig. 1C). Importantly, γ-selectivity for both primary and methylene C–H bonds is achieved on acyclic and cyclic alcohols in the presence of β-C–H bonds (Fig. 1D). The reversal of site selectivity can be rationalized by favoring the 6-membered over the 5-membered cyclopalladation through geometric directing group design, as supported by the isolation of the intermediate and computational analysis.

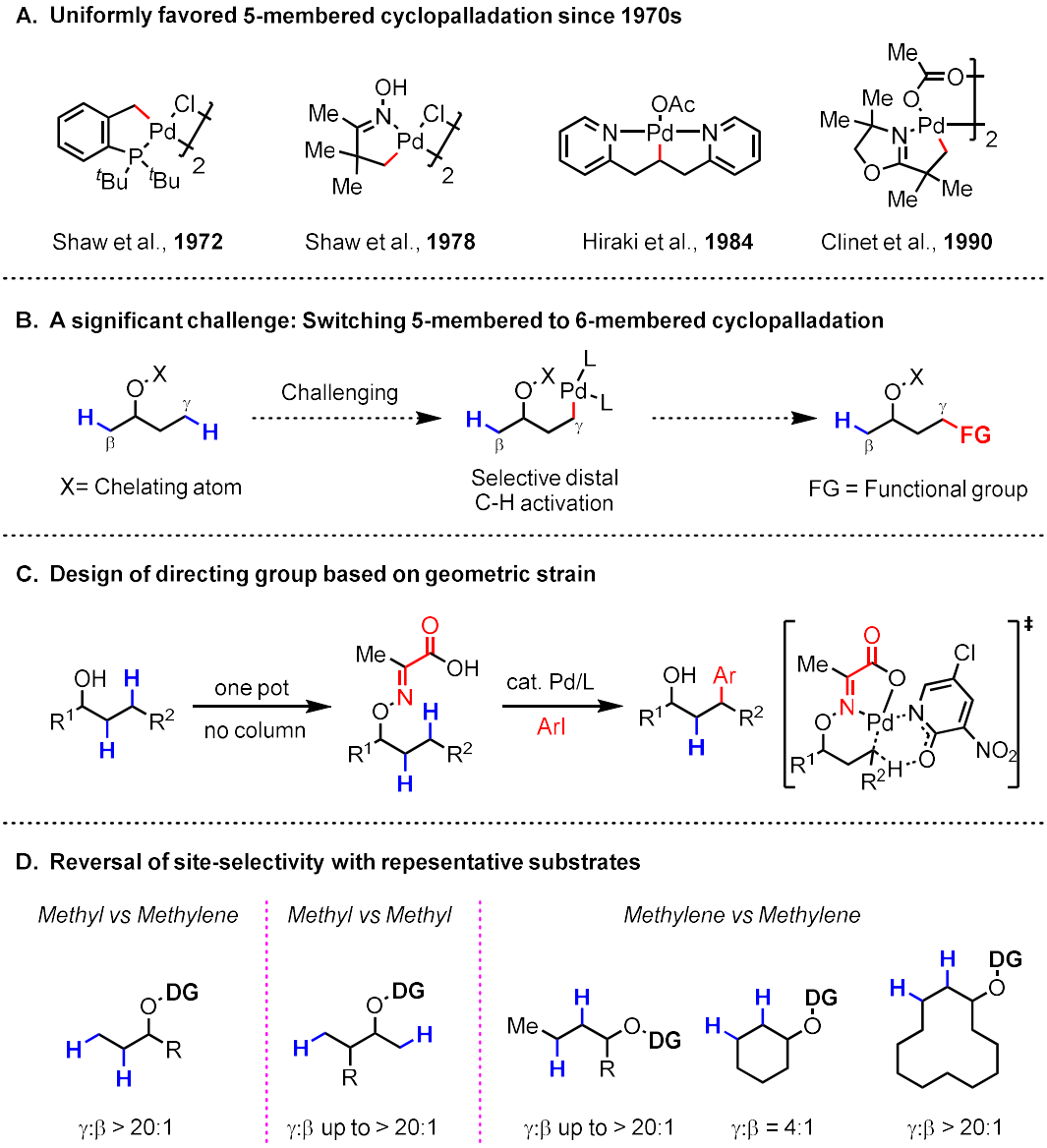
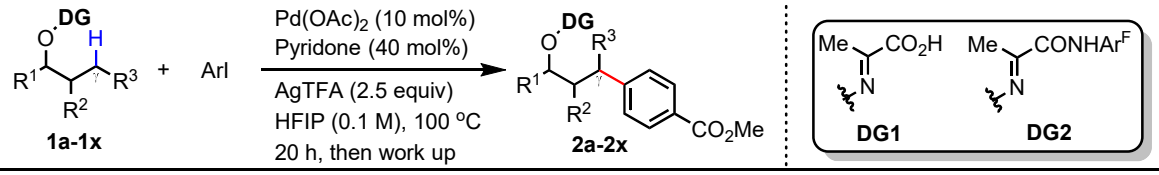


Fig. 1. Reversing the site-selectivity for C(sp^3)–H activation of aliphatic alcohol. (**A**) Uniformly favored 5-membered cyclopalladation since 1970s. (**B**) A significant challenge: Switching 5-membered to 6-membered cyclopalladation. (**C**) Design of directing group based on geometric strain. (**D**) Reversal of site-selectivity with representative substrates.

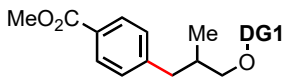
We selected alcohol substrates to search for a practical directing group and catalyst system that can reverse the commonly favored β-selectivity to γ-selectivity because: a) alcohols are abundant and synthetically versatile starting materials (*30*); b) γ-C–H activation of alcohols

using Pd insertion has not been reported to date. The first challenge is to realize the palladation of γ-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 (*22, 31*), was crucial for the C(sp^3)–H arylation of aliphatic alcohol when using **DG1** as the directing group (Fig. 1B). Arylation product **2a** was obtained in 75% isolated yield (mono:di = 2.3:1). 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(sp^3)–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,** Fig. 2). Secondary alcohols are also reactive, affording the arylation products in good yields (**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-

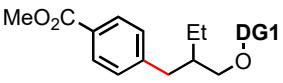
fluorophenyl iodide (**3u**); *poly*-substituted aryl iodides provided the arylation product in good yields (**3v**, **3w**). 5-iodoindole was also a compatible substrate, providing the product in 62% yield (**3x**).



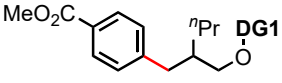
Alcohols containing no β-primary or methylene C-H bonds:



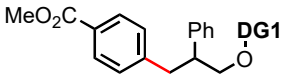
2a: 75% (mono:di = 2.3:1)



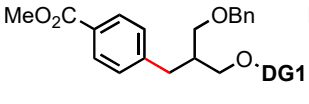
2b: 69%



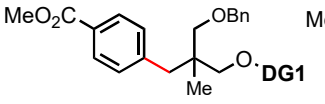
2c: 72%



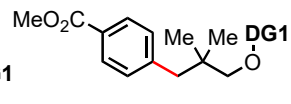
2d: 57%



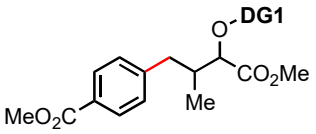
2e: 85%



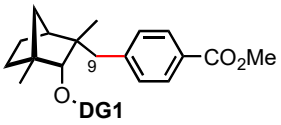
2f: 72%



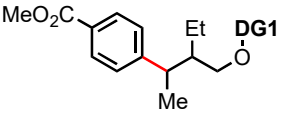
2g: 94% (mono:di = 4:1)



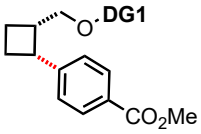
2h: 68% (mono:di = 2.6:1)



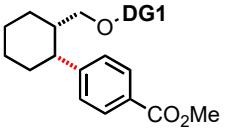
Fenchol (**2i**): 84%



2j: 54%

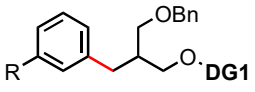


2k: 48%

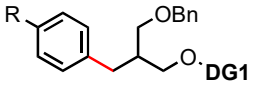


2l: 52% (mono:di = 2:1)

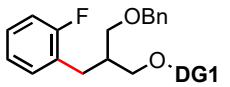
Aryl iodide scope:



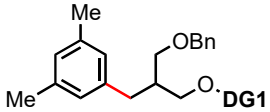
R = H	**3a**, 76% yield
Me	**3b**, 73% yield
OMe	**3c**, 69% yield
CF_3	**3d**, 79% yield
CHO	**3e**, 83% yield
NO_2	**3f**, 77% yield
CO_2Me	**3g**, 71% yield
COPh	**3h**, 75% yield
Cl	**3i**, 81% yield
I	**3j**, 58% yield



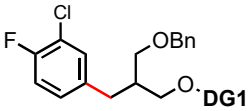
R = F	**3k**, 77% yield
Cl	**3l**, 75% yield
Br	**3m**, 64% yield
NO_2	**3n**, 82% yield
Ph	**3o**, 72% yield
CHO	**3p**, 78% yield
CO_2Me	**3q**, 85% yield
Me	**3r**, 68% yield
OMe	**3s**, 67% yield
OCF_3	**3t**, 56% yield



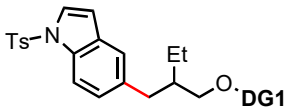
3u: 54%



3v: 66%



3w: 75%



3x: 62%

Fig. 2. γ-Arylation of aliphatic alcohols. Ar^F, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl. The products for **DG1** tethered substrates were isolated in their methyl ester form. Diastereomeric ratio was determined by crude ^1H NMR spectroscopy.

With this effective protocol for γ-C–H arylation in hand, we began to address a fundamental challenge, namely, achieving distal selectivity in C(sp^3)–H activation by favoring six-membered cyclopalladation over the five-membered process. Such a switch of regioselectivity could double the utility of current C(sp^3)–H activation reactions based on five-membered cyclopalladation by enabling the functionalization of many previously inaccessible C–H bonds. Notably, a majority 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 (γ/β =2:1) when using **DG1** as the directing group. Through further tuning of the directing group (see supplementary materials), we found that the amide directing group derived from 2,3,5,6-tetrafluoro-4-CF_3-phenyl amine (**DG2**) afforded the γ-C(sp^3)–H bond arylation exclusively in 72% yield (**5b,** Fig. 3). Thus we have developed two protocols for γ-C–H activation of alcohols: **DG1** with pyridone ligand displayed higher reactivity but lower selectivity (γ/β =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 materials). Remarkably, despite the fact that the β-primary C–H bonds are typically far more reactive than the γ-primary C–H bonds (>20:1, *28, 29*), 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 transannular 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 transannular 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.

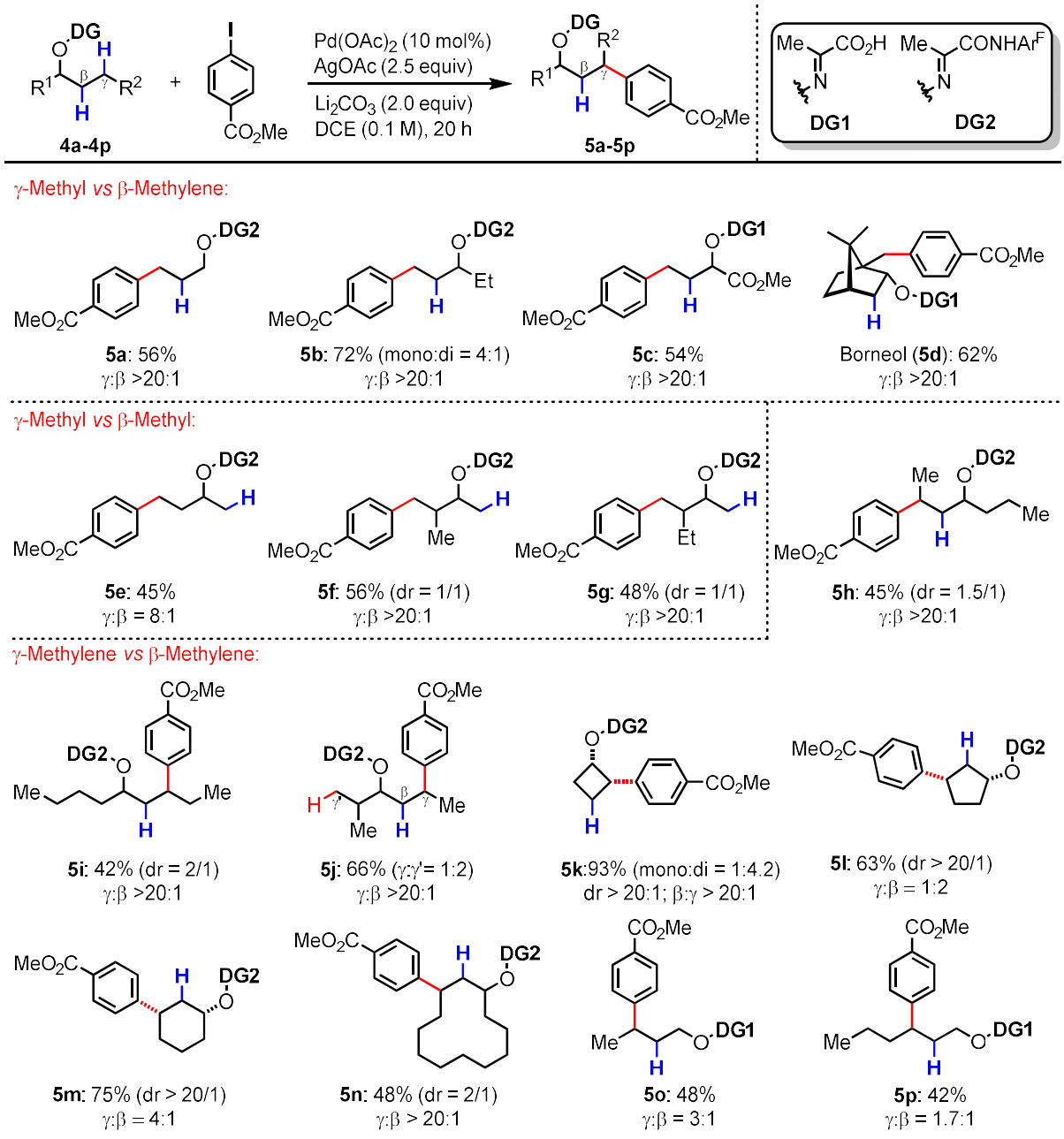


Fig. 3. Alcohols containing β-primary or methylene C–H bonds. Ar^F, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl. The products for **DG1** tethered substrates were isolated in their methyl ester form. Diastereomeric values were determined by crude ^{1}H NMR spectroscopy.

To gain further insight into the mechanism for γ-selectivity, substrates **1g** and **7** were subjected to cyclopalladation in a 1:1 ratio. Interestingly, only the 6-membered palladacyle **6** was

isolated in 62% yield; this structure was characterized by X-ray diffraction. By contrast, 5-membered palladacycle **8** was not observed, suggesting the pyruvic acid derived directing group in this work favors 6-membered cyclopalladation exclusively over 5-membered cyclopalladation (Fig. 4A). Moreover, the 6-membered palladacycle **6** reacted with aryl iodide to yield product **2g** under the established conditions. DFT calculations on substrate **4o** also revealed that the 6-membered cyclopalladation intermediate is indeed more stable than the 5-membered one thermodynamically. Kinetically, the conventional strong preference for 5-membered cyclopalladation process, as previously computed to have a 5 kcal/mol lower energy transition state than the 6-membered cyclopalladation process (*32*), is also significantly reduced to 1 kcal/mol using our directing group (see supplementary materials). Finally, we found 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 (Fig. 4B).

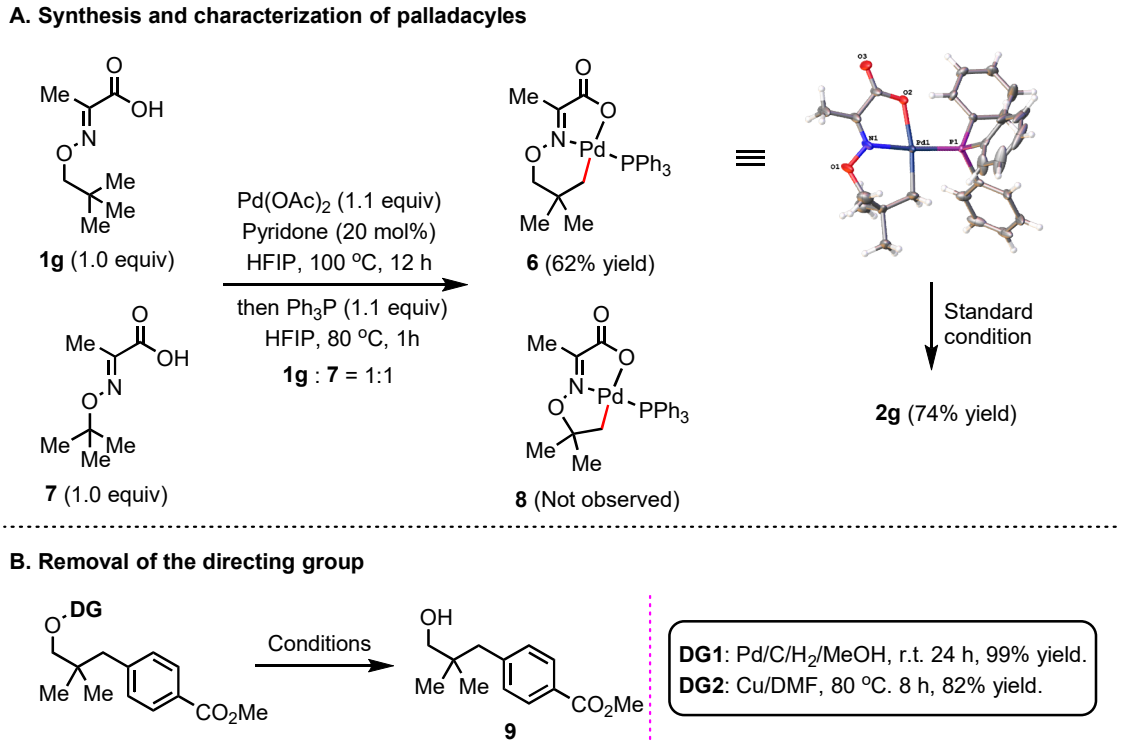


Fig. 4. Mechanistic study and removal of directing group. (**A**) Synthesis and characterization of palladacycles. (**B**) Removal of the directing group.

In conclusion, we have developed a new protocol for functionalization of distal C(sp^3)–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(sp^3)–H functionalization of other synthetically or medicinally useful compounds.

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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.

Supplementary Materials:

Materials and Methods

Tables S1-S4

X-ray Crystallographic Data

Computational Studies

NMR Spectra

References (*33-44*)