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

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One of the core barriers to developing C–H activation reactions is the ability to distinguish between 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-pyridone 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. A competition experiment between the 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(sp^3)–H activation.

The development of C–H activation reactions as new retrosynthetic disconnections could offer a multitude of new synthetic strategies due to the abundance of positionally diverse C–H bonds[1,2]. However, the great resemblance between these C–H bonds in terms of bond strength and electronic properties presents a tremendous obstacle for achieving regioselectivity. Recently, remote C(sp^2)–H bonds have been selectively activated in the presence of proximate ones through recognition of distance and molecular geometry[3,4], but achieving such unconventional site selectivity with C(sp^3)–H bonds remains a challenge. This difficulty escalates with metallation chemistry because in such processes the numerous primary or secondary C–H bonds cannot be distinguished by the metal. For example, despite recent advances in developing a wide range of palladium-catalysed 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[5–12] (Fig. 1a). Therefore, it is fundamentally important to develop strategies to change the selectivity of the key metallation step from favouring five-membered to six-membered cyclopalladation (Fig. 1b). Such strategies will allow palladium catalysts to preferentially functionalize widespread carbon centres 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 favoured over its six-membered or larger-sized counterparts since its realization in the1970s (Fig. 1a)[13–16]. As a consequence, distal C(sp^3)–H functionalization via a six-membered palladacycle is limited to the following rare examples: (1) when five-membered cyclopalladation is not possible due to the lack of primary or secondary C–H bonds at the appropriate carbon[17–21]; and (2) 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—this single observation is limited to more reactive methyl C–H bonds[22]. Notably, iridium-catalysed 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 oxasiloane formation from the five-membered cycloiridation is disfavoured[23,24]. In this context, intermolecular γ-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 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 3-nitro-5-chloro-2-pyridone ligand (**1**). The rationale of our design for a directing group is based on the ring strain of the bicyclic palladacycles. Although previous bidentate directing groups also involve bicyclic palladacycles, the key to our design is the incorporation of 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 favours the six-membered cyclopalladation. It is well known that multiple sp^2 centres on a small ring will increase the ring strain[29] (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).

Results and discussion

We selected alcohol substrates in our search for a practical directing group and catalyst system that can reverse the commonly favoured β-selectivity to γ-selectivity because alcohols are abundant and synthetically versatile starting materials[30] and γ-C–H activation of alcohols using palladium insertion has not been reported so far. 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 (**2a**), which contained 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 is easily purified by basic and acidic work-up without column. No arylation product was observed under various conditions. We have previously shown that ligands can enable or substantially promote both C(sp^2)–H and C(sp^3)–H activation reactions[11]. Thus, several different classes of ligands were screened under various conditions. We found that *N*-acetyl-protected amino acids and acetyl-protected aminomethyl oxazolines promoted the C–H

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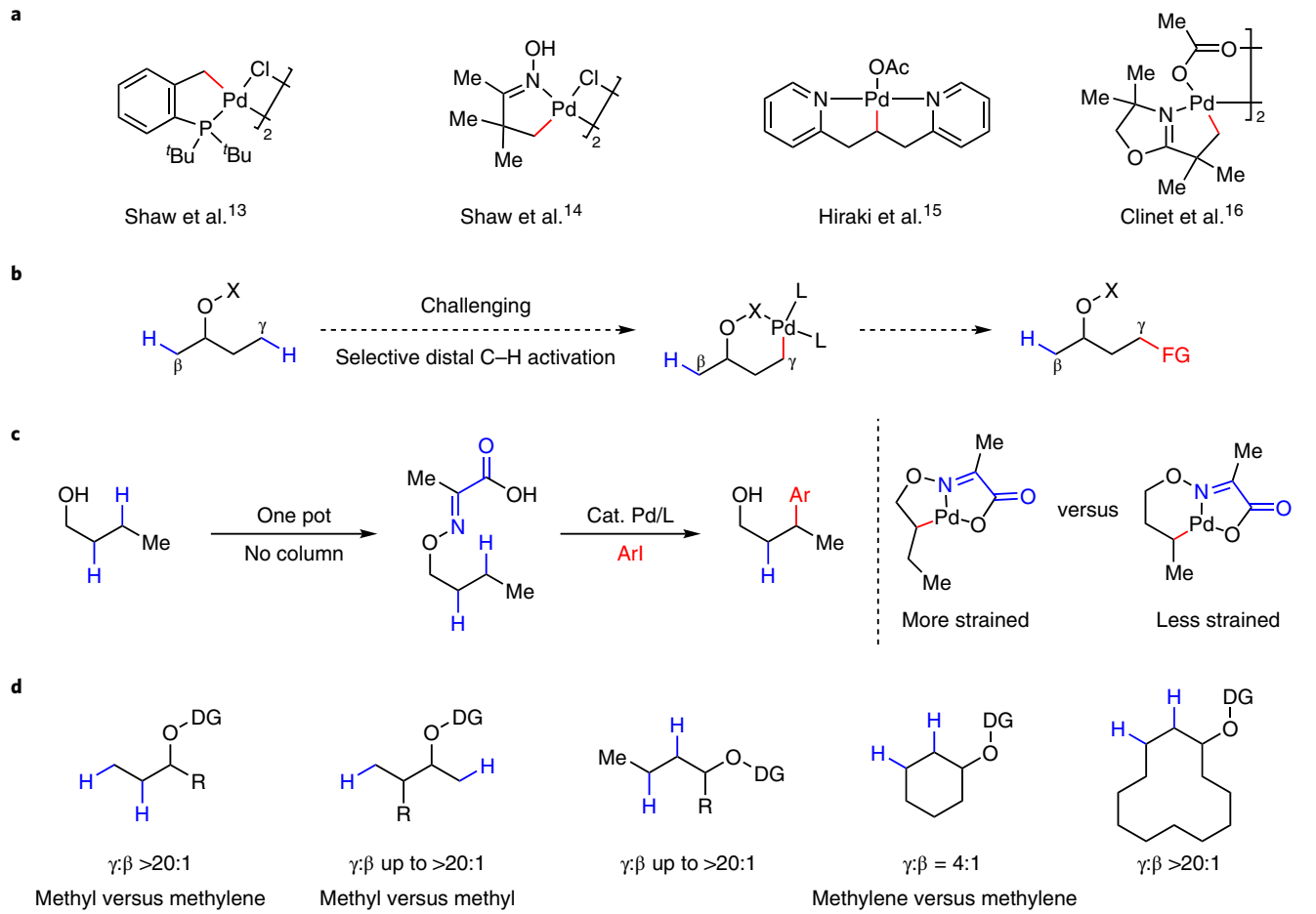


Fig. 1 | Reversing the site-selectivity for C(sp^3)–H activation of aliphatic alcohols. a, Examples of uniformly favoured five-membered cyclopalladations since the 1970s. **b**, Changing five-membered to six-membered cyclopalladation. X, chelating atom; L, ligand; FG, functional group. **c**, The design of the directing group is based on geometric strain. The introduction of multiple double bonds to the directing group makes the five-membered palladacycle more strained than the six-membered counterpart, thus making the selective six-membered cyclopalladation possible. **d**, Reversal of site selectivity with representative substrates. This new directing group, in combination with the pyridone ligand, provides good γ-selectivity with a broad substrate scope that includes primary and methylene C(sp^3)–H bonds.

arylation to some extent, but the yield was very low (<20%). When pyridine-type ligands were employed, no reaction was observed (see Supplementary Table 1). We then turned our attention to the electron-deficient pyridone ligands that were previously found to be beneficial for both C(sp^2)–H and C(sp^3)–H functionalization[21,31]. The γ-arylation product was obtained in 66% yield when 5-trifluoromethyl-2-pyridone was used as the ligand. Through extensive ligand screening we discovered that **1** was best for the C(sp^3)–H arylation of an aliphatic alcohol when using **DG1**; arylation products **3a** and **3a′** were obtained in 75% isolated yield (the mono:di ratio was 2.3:1) (Table 1). Other pyridone ligands that bear electron-donating groups on the pyridine ring were not effective enough for the reaction (see Supplementary Table 1). Electron-deficient 2-pyridones not only stabilize the palladium catalyst but also lower the transition-state energy of the C–H cleavage step[31]. To examine the robustness of this γ-C–H arylation protocol, we subjected a series of alcohol substrates that bear no β-primary or β-methylene C(sp^3)–H bonds to the standard conditions (Table 1). We found that methyl groups in primary alcohols that undergo substitution at the β-position were arylated smoothly to give the desired products in good to excellent yields (**3a**–**3g**). Secondary alcohols are also reactive, affording the arylation products in good yields (**3h** and **3h′**). Interestingly, the naturally occurring enantiopure (1R)-*endo*-(+)-fenchol was arylated specifically at the C9 position in 84% yield (**3i**). The efficiency of this protocol was further showcased by arylation of γ-methylene C–H bonds in both acyclic and cyclic alcohols (**3j**–**3l**). A wide range of aryl iodides were compatible, affording the desired γ-arylation product in good yields (Table 1). For example, a series of *meta*-substituted electrophiles, including electron-donating (**4a**–**4c**) and electron-withdrawing (**4d**–**4h**) groups, gave the products in good to excellent yields; halides were compatible, providing the arylation products in good yields (**4i**, **4j**). A series of *para*-substituted aryl iodides also afforded the products in good to excellent yields (**4k**–**4s**). *Ortho*-substituted aryl iodides were not reactive enough under the standard conditions, with the exception of 2-fluorophenyl iodide (**4t**); polysubstituted aryl iodides provided the arylation product in good yields (**4u**, **4v**). 5-Iodoindole was a compatible substrate, providing the product in 62% yield (**4w**).

Using this effective protocol, we began to address the fundamental challenge of achieving distal selectivity in C(sp^3)–H activation by favouring six-membered cyclopalladation over the five-membered process. Such a change of regioselectivity could double the utility of current C(sp^3)–H activation reactions that are based on five-membered cyclopalladation by enabling the functionalization of many previously inaccessible C–H bonds. Most of the alcohol substrates contain both β- and γ- primary and methylene C–H bonds.

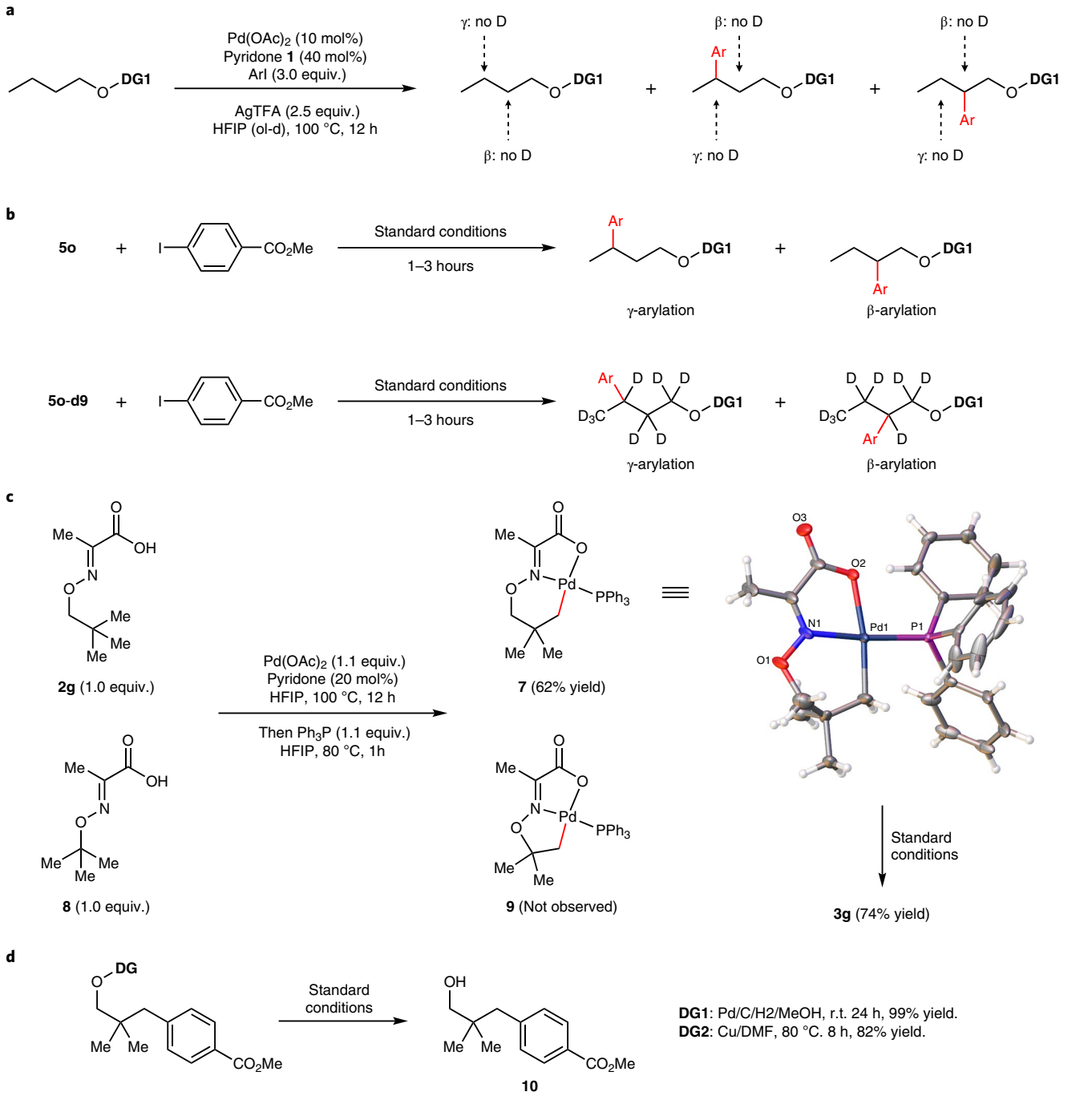
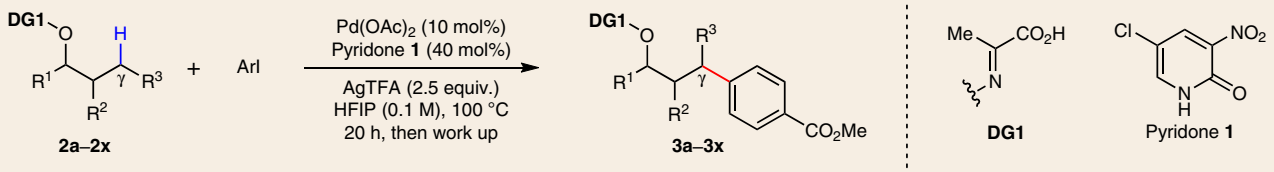


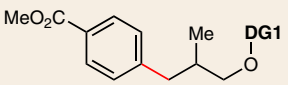
Fig. 2 | Mechanistic study and removal of directing group. a, The deuterium incorporation experiment. Ar, *p*-MeO_2C-C_6H_4I. HFIP (ol-d), $(CF_3)_2CHOD$. **b**, KIE experiments. **5o-d9**, $CD_3CD_2CD_2CD_2O$**DG1**. $KIE_\gamma = 4.4$, $KIE_\beta = 2.7$, $k_\gamma/k_\beta = 4.1$. KIE experiments show that the C–H cleavage step was the rate-determining step for both β- and γ-C–H arylation, and the kinetic experiments show that the initial rate of γ-C(sp^3)–H arylation is faster than β-C(sp^3)–H bond **c**, Synthesis and characterization of palladacycles. Competition experiment of five- and six-membered cyclopalladation show that only the six-membered palladacycle is formed. **d**, Removal of the directing group.

Considering that primary C–H bonds are more reactive than methylene C–H bonds, 3-pentanol—which contains 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**. The yield was low under basic conditions (17%), although the regioselectivty was slightly better (γ:β = 7:1) (see Supplementary Table 2). We then tested various directing groups that contain different chelating moieties, including previously reported directing groups for alcohols[27,28]. Unfortunately, these alterations resulted in complete loss of reactivity under either acidic or basic conditions. Through further tuning of the directing group (see Supplementary Table 2), 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 under basic conditions (**6b** and **6b′**, Table 2). When **DG2** was used, the ligand was not crucial for the reaction. 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

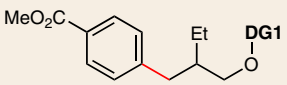
Table 1 | γ-Arylation of aliphatic alcohols containing no active β-C–H bonds.



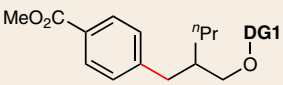
Alcohols containing no β-primary or methylene C–H bonds:



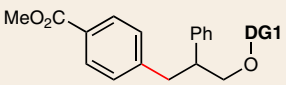
3a, 52% mono
3a', 23% di



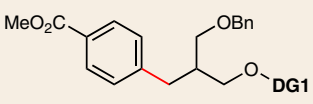
3b, 69%



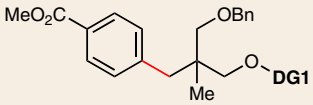
3c, 72%



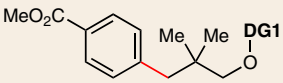
3d, 57%



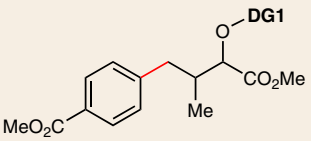
3e, 85%



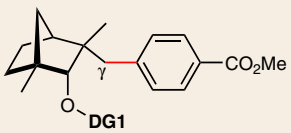
3f, 72%



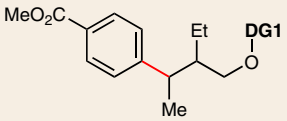
3g, 75% mono
3g', 19% di



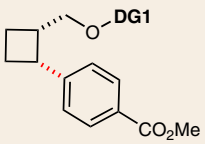
3h, 49% mono
3h', 20% di



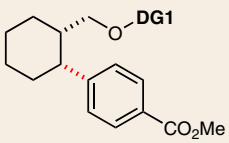
Fenchol (**3i**), 84%



3j, 54%

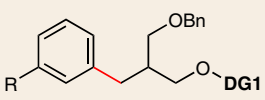


3k, 48%

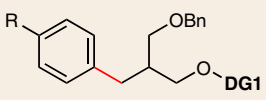


3l, 35% mono
3l', 17% di

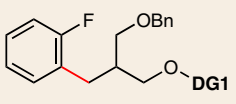
Aryl iodide scope:



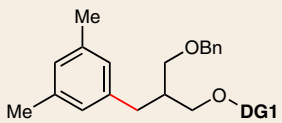
R =	H	**4a**, 76% yield
	Me	**4b**, 73% yield
	OMe	**4c**, 69% yield
	CF_3	**4d**, 79% yield
	CHO	**4e**, 83% yield
	NO_2	**4f**, 77% yield
	CO_2Me	**4g**, 71% yield
	COPh	**4h**, 75% yield
	Cl	**4i**, 81% yield
	I	**4j**, 58% yield



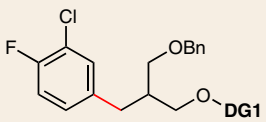
R =	F	**4k**, 77% yield
	Cl	**4l**, 75% yield
	Br	**4m**, 64% yield
	NO_2	**4n**, 82% yield
	Ph	**4o**, 72% yield
	CHO	**4p**, 78% yield
	Me	**4q**, 68% yield
	OMe	**4r**, 67% yield
	OCF_3	**4s**, 56% yield



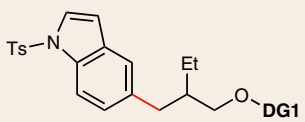
4t, 54%



4u, 66%



4v, 75%



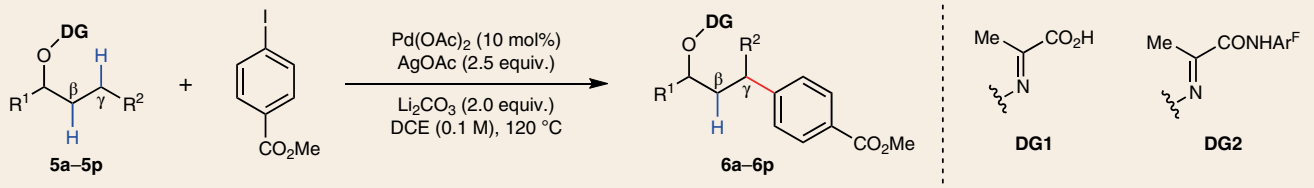
4w, 62%

All of the yields were isolated yields. The products were isolated after esterification of **DG1** (for details see the General procedure D in the Supplementary Information). The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude mixture. ArI, methyl 4-iodobenzoate; AgTFA, silver trifluoroacetate; HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol.

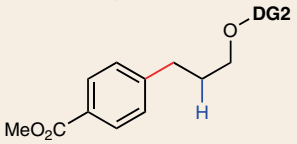
yields but with exclusive γ-selectivity. These two designed L-, X-type directing groups, utilized in conjunction with electron-deficient pyridone ligands, are capable of enabling the γ-C–H arylation, as a wide range of other directing groups and ligands (and combinations of thereof) are ineffective (see Supplementary Table 2). 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 cyclometallation was realized using our protocol (**6e**–**6g**). Highly γ-selective arylation of alcohol substrates **5a**–**5d** 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 metallation has not been reported so far; and (2) steric demand for γ-methylene C–H bond and β-methylene C–H bond metallation are similar. Surprisingly, a substrate derived from 4-heptanol that contains four β- and four γ-methylene C–H bonds afforded exclusive γ-selectivity in 45% yield (**6h**), other similar substrates afforded the same exclusive γ-selectivity (**6i**, **6j**). This reversal of site selectivity was also achieved with cyclic alcohol substrates (**6m**, **6n**). Unsurprisingly, γ-C–H arylation is less favoured with smaller rings due to the rigid geometric strain. While both β- and γ-arylated products were obtained with a cyclopentanol substrate affording a ratio of 2:1 in favour of β-arylation (**6l**), a cyclobutanol substrate afforded β-arylation product in 93% yield due to the

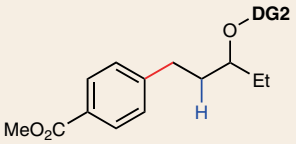
Table 2 | Alcohols containing β-primary or methylene C–H bonds.



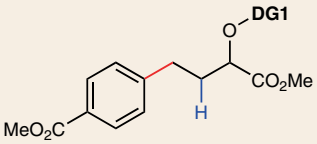
γ-Methyl versus β-Methylene:



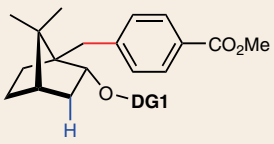
6a, 56%
γ:β >20:1



6b, 58% mono, **6b'**, 14% di
γ:β >20:1

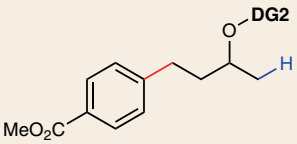


6c, 54%
γ:β >20:1

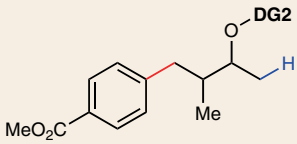


Borneol (**6d**), 62%
γ:β >20:1

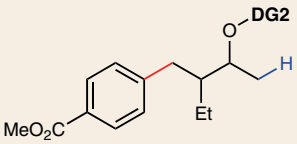
γ-Methyl versus β-Methyl:



6e, 45%
γ:β = 8:1

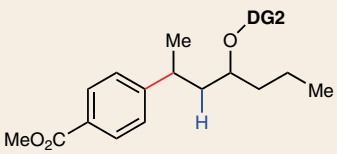


6f, 56% (d.r. = 1/1)
γ:β >20:1

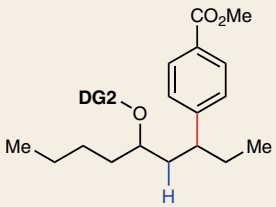


6g, 48% (d.r. = 1:1)
γ:β >20:1

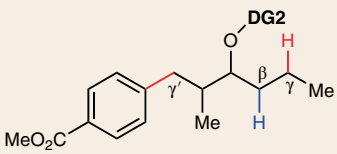
γ-Methylene versus β-Methylene:



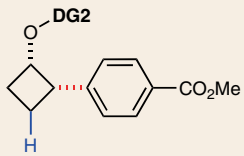
6h, 45% (d.r. = 1.5:1)
γ:β >20:1



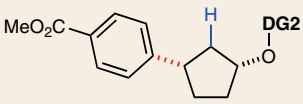
6i, 42% (d.r. = 2:1)
γ:β >20:1



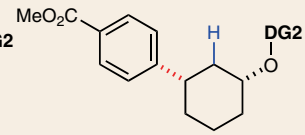
6j, 66% (γ′:γ = 2:1)
(γ+γ′):β >20:1



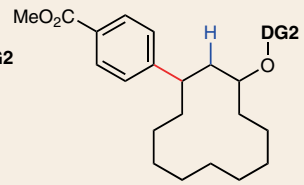
6k,19% mono, **6k'**, 75% di
d.r. >20:1; β:γ >20:1



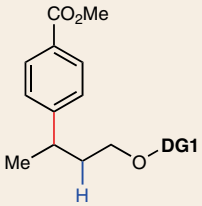
6l, 63% (d.r. >20:1)
γ:β = 1:2



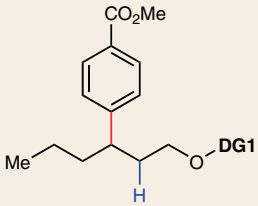
6m, 75% (d.r. >20:1)
γ:β = 4:1



6n, 48% (d.r. = 2:1)
γ:β >20:1



6o, 48%
γ:β = 3:1



6p, 42%
γ:β = 1.7:1

The conditions for products **6c**, **6d**, **6o** and **6p** were the same as those in Table 1 (see Supplementary Information, General procedure D). All of the yields were isolated yields. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the crude mixture. The γ:β ratios of **6o** and **6p** were determined by ^{1}H NMR spectroscopy of the two isomer mixtures. Ar^F, 2,3,5,6-tetrafluoro-4-(trifluoromethyl) phenyl; DCE, 1, 2-dichloroethane.

extreme geometric strain (**6k**). Finally, γ-arylation is preferred over β-arylation with primary alcohol substrates (**6o**, **6p**), albeit in lower selectivity (γ:β = 3:1). This result, although not yet 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. The lack of D-incorporation suggests that the arylation step is sufficiently fast to outcompete the reversibility of the C–H activation step (Fig. 2a). Kinetic isotope effect (KIE) experiments showed that the C–H cleavage step was rate determining for both β- and γ-C–H arylation ($KIE_\gamma = 4.4$, $KIE_\beta = 2.7$, Fig. 2b). The kinetic experiments also show that the initial rate of γ-C(sp^3)–H arylation is faster than for the β-C(sp^3)–H bond ($k_\gamma/k_\beta = 4.1$, Fig. 2b), 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 the palladacycle with the aryl iodide. To directly compare the cyclopalladation of β- and γ-C–H bonds, substrates **2g** and **8** were subjected to cyclopalladation conditions in a 1:1 ratio. Only six-membered palladacyle **7** was isolated in 62% yield; this structure was characterized

by X-ray diffraction. By contrast, five-membered palladacycle **9** was not observed. The palladacycle **7** was able to react with aryl iodide to yield product **3g** under the established conditions (Fig. 2c). Finally, we found the methyl ester of **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. 2d).

Conclusion

In summary, we have developed a protocol for the functionalization of distal C(sp^3)–H bonds of aliphatic alcohols. Conventionally favoured five-membered cyclopalladation was reversed to favour six-membered cyclopalladation by introducing a geometrically strained directing group. This protocol works with a wide range of substrates and tolerates a series of functional groups. A simple procedure for both the installation and removal of the directing group renders this protocol highly practical. The strategy disclosed herein to favour 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.

Methods

General procedure for γ-arylation of DG1-tethered alcohols. **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) were added to a 10 ml reaction vial with a magnetic stir bar, 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 h. The mixture was cooled to room temperature, diluted with 2 ml of ethyl acetate and filtered through a pad of Celite, and then washed with another 2 ml of ethyl acetate. The filtrate was concentrated and redissolved with 5 ml of methanol, cooled with an ice bath, and then sulfonyl chloride (0.2 ml) was added slowly. The resulting mixture was stirred at room temperature for 30 min and 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 the Supplementary Information.

General procedure for γ-arylation of DG2-tethered alcohols. **DG2**-tethered alcohol substrate (0.1 mmol), aryl iodide (0.3 mmol), palladium acetate (0.01 mmol), lithium carbonate (0.2 mmol) and silver acetate (0.25 mmol) were added to a 10-ml reaction vial with a magnetic stir bar, the mixture was dissolved with 1 ml of 1,2-dichloroethane and then the vial was capped. The reaction mixture was stirred at 120 °C for 20 h. After cooling to room temperature, the mixture was diluted with 2 ml of ethyl acetate and filtered through a pad of Celite, and then washed with another 2 ml of ethyl acetate. The filtrate was concentrated and the residue was purified by preparative thin-layer chromatography to get the arylation product. Full experimental details and characterization of compounds are given in the Supplementary Information.

Data availability

The data supporting the findings of this study are available in the article and its Supplementary Information. Metrical parameters for the structure of **7** (see Supplementary Information) are available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/) under reference no. CCDC-1872396.

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Author contributions

J.-Q.Y. and G.X. conceived the concept. G.X. developed the distal C(sp^3)–H arylation for aliphatic alcohols. G.X. and J.W. synthesized the alcohol substrates and investigated the scope. G.X., Z.L. and L.L. conducted the experiments for aryl iodide scope. G.X. and P.V. conducted the mechanistic studies. J.-Q.Y. supervised the project.

Competing interests

The authors declare no competing interests.

Additional information

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