



C–H Activation Hot Paper

Ligand-Enabled β -Methylene $C(sp^3)$ -H Arylation of Masked Aliphatic Alcohols

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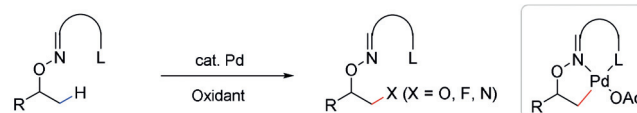
Abstract: Despite recent advances, reactivity and site-selectivity remain significant obstacles for the practical application of $C(sp^3)$ -H bond functionalization methods. Here, we describe a system that combines a salicylic-aldehyde-derived L,X-type directing group with an electron-deficient 2-pyridone ligand to enable the β -methylene $C(sp^3)$ -H arylation of aliphatic alcohols, which has not been possible previously. Notably, this protocol is compatible with heterocycles embedded in both alcohol substrates and aryl coupling partners. A site- and stereo-specific annulation of dihydrocholesterol and the synthesis of a key intermediate of enflitazone illustrate the practicality of this method.

Palladium-catalyzed $C(sp^3)$ -H functionalization reactions are uniquely suited for diversity-oriented synthesis and late-stage diversification, owing to the versatile reactivity of the intermediate carbon–palladium bonds for forging a wide range of carbon–carbon and carbon–heteroatom bonds.^[1] However, most reported palladium-catalyzed $C(sp^3)$ -H arylation reactions present three significant obstacles that limit their practical application: (1) secondary $C(sp^3)$ -H bonds are less readily functionalized than the more reactive and less hindered primary C–H bonds;^[2] (2) aza-heterocyclic substrates, in which the nitrogen atom may provide an extra coordination site with palladium, can suffer from sluggish C–H activation;^[3] (3) aza-heteroaryl iodides remain largely inefficient coupling partners for $C(sp^3)$ -H functionalization.^[4] Generally, efforts to address these limitations have focused on carboxylic acids^[3a–e] and amines^[3c,4a] (or derivatives thereof) as C–H activation substrates. In comparison, fewer methods and practical directing groups exist to achieve the C–H functionalization of aliphatic alcohols, despite the abundance of this motif among therapeutically relevant natural and unnatural products.^[5]

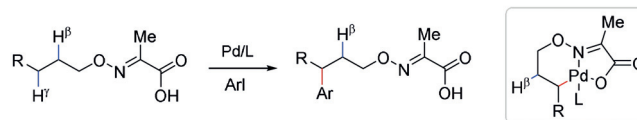
Perhaps owing to the weak coordination of transition metals with the hydroxyl moiety, C–H activation reactions on

free alcohol substrates are limited to sp^2 C–H bonds^[6] or photoredox processes where site-selectivity is dictated by 1,5-hydrogen-atom transfer (HAT).^[7] Recently, iridium-catalyzed intramolecular $C(sp^3)$ -H silylation of alcohols using a tethered silyl hydride have been reported.^[8] A common strategy to promote selective C–H metalation consists in preinstalling an external chelating group onto the hydroxyl group, which both accelerates and imparts selectivity to a critical step of cyclometallation. We and others employed various directing groups for palladium-catalyzed $C(sp^3)$ -H oxidation,^[9] fluorination,^[10] amination,^[11] carboxylation and olefination^[12] of alcohol substrates. Notably, these reactions are largely limited to primary C–H bonds with a few exceptional examples of fluorination and acetoxylation^[9a,10] (Scheme 1 a).

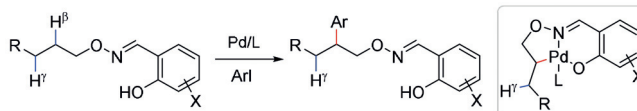
a. β -C-H oxidation: L,L-type directing group, limited to C-X bond formation



b. γ -selective C-H arylation: L,X-type directing group, C-C bond formation



c. β -selective C-H arylation (this work): L,X-type directing group



Scheme 1. Versatile $C(sp^3)$ -H functionalizations of aliphatic alcohols.

These advances notwithstanding, examples of C–C bond formation reactions based on aliphatic-alcohol C–H bond activation remain limited. Recently, we reported a method for γ -C–H arylation of aliphatic alcohols via the incorporation of directing group and 2-pyridone ligand (Scheme 1 b). Although the reaction proceeds with certain secondary C–H bonds (specifically, cycloalkane methylene C–H), it remains incompatible with aza-heterocyclic substrates and heteroaryl iodides.^[13] The γ -selectivity in this reaction is thought to arise from the preference, upon C–H metalation for a [5,6]-fused palladacycle intermediate (Scheme 1 b). We thus hypothesized that the choice of a directing group that would instead form a [6,5]-bicyclic palladacycle intermediate, would facilitate β -selective C–H metalation (Scheme 1 c).

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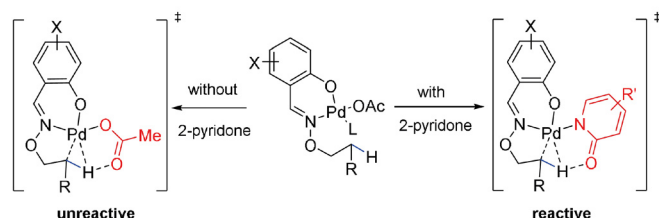
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In addition, by introducing an external 2-pyridone ligand, which has been proved to significantly lower the transition state energy of C–H activation steps,^[14] less reactive C(sp³)–H bonds (e.g., secondary, tertiary) would be activated (Figure 1 a). Because the β -C–H arylation of aliphatic alcohols at non-primary sites still remains unexplored, developing such a transformation could effectively offer a positionally diverse C–H bond editing method.

a. Ligand Acceleration Effect



b. One-pot Installation of directing group

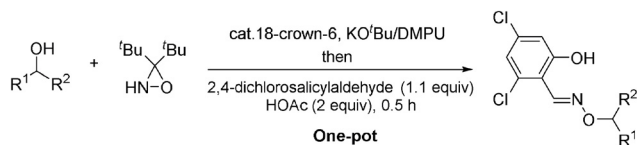


Figure 1. Ligand acceleration effect and directing group installation.

To evaluate the feasibility of our approach, we first attempted the β -arylation of cyclopentanol employing a range of aldoxime- and alkoxamide-based directing groups. A representative example of directing group installation, achieved in a single operation from the corresponding alcohol, is depicted in Figure 1 b, and results of the directing group study are summarized in Table 1 a. Cyclopentanol had indeed shown limited reactivity at the β -methylene in our previous studies (Table 1 a, **DG1**, β : γ = 2:1);^[13] moreover, some β -methyl C–H arylations were also reported using a closely related directing group.^[15] Two sets of reaction conditions that had proved effective in our former work^[13] were selected for the initial directing-group screening. These conditions differ, notably, in the reagent used to facilitate the concerted metalation-deprotonation step: lithium carbonate (2.0 equiv, condition A) or 3-nitro-5-chloro-2-pyridone (**L1**, 40 mol %, condition B). Directing groups based on pyridine-2-carboxylic acid (**DG2**) or quinoline-8-carboxylic acid motif (**DG3**), frequently used in directed C–H activations, failed to afford the desired product (**2**) under the attempted conditions. To our delight, a salicylic-aldehyde-derived directing group (**DG4**), inert under condition A, under condition B led to the formation of β -arylation product **2** in 44% yield without evidence of γ -arylation product in the crude reaction mixture (¹H NMR). Given this encouraging result, we screened several other salicylic aldehydes with different substituents on the aromatic ring (**DG5–DG9**): dichloro-derivative **DG9** was found to be the most effective directing group, resulting in 56% yield of **2**. Notably, none of the examples that employed salicylic-aldehyde-derived directing groups led to observable quantities of γ -arylation product. In addition, methylation of the free hydroxyl group (**DG10**) abolished

Table 1: Directing group and ligand screening.^[a]

Directing Group	Condition	Yield (%)	β : γ Ratio
DG1	Condition A	63%	2:1
DG2	Condition A or B	N.R.	
DG3	Condition A or B	N.R.	
DG4	Condition B	44%	> 20:1
DG5	Condition B	17%	> 20:1
DG6	Condition B	34%	> 20:1
DG7	Condition B	38%	> 20:1
DG8	Condition B	49%	> 20:1
DG9	Condition B	56%	> 20:1
DG10	Condition A or B	N.R.	

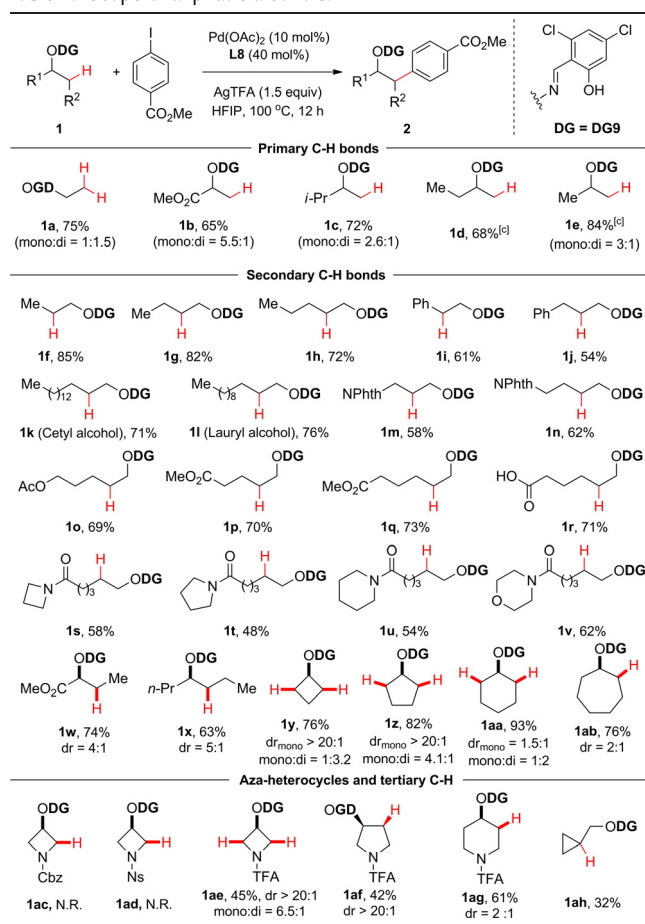
Ligand	Yield (%)
L1	38%
L2	18%
L3	58%
L4	52%
L5	N.R.
L6	56%
L7	55%
L8	72%
L9	60%
L10	62%
L11	4%
L12	N.R.
L13	6%
L14	N.R.
No Ligand	N.R.

[a] Yields were determined by ¹H NMR using dibromomethane as internal standard. Condition A: Substrate **1** (0.1 mmol), aryl iodide (0.3 mmol), Pd(OAc)₂ (10 mol %), AgOAc (2.5 equiv), Li₂CO₃ (2.0 equiv) in DCE (1.0 mL), 120°C, 24 h; Condition B: Substrate **1** (0.1 mmol), aryl iodide (0.3 mmol), Pd(OAc)₂ (10 mol %), Ligand (40 mol %), AgTFA (1.5 equiv), in HFIP (1.0 mL), 100°C, 4 h. [b] Ligand **L6** was used with condition B. [c] No reaction under condition B. [d] No reaction under condition A. [e] Using condition B and **DG9** as directing group.

reactivity, indicating that L,X-type directing groups are crucial to the success of this reaction.

In order to further increase the efficiency of this reaction, we investigated the effect of the 2-pyridone ligand (Table 1 b). We first found that no reaction occurred in its absence, both evidencing its crucial role and indicating an opportunity for reaction optimization. Indeed, after screening a series of 2-pyridone ligands, we found that electron-withdrawing groups at C-4 or C-5 position generally promoted the reaction, although with moderate yields (**L1–L4**); while substitution at C-6 position did not give any product (**L5**). Electron-withdrawing groups at both C-3 and C-5 resulted in better reactivity; among these, **L8** was the most reactive and gave 72% yield. Other types of ligands such as oxazoline-acetamide (**L12**), acetylglycine (**L13**) and dibenzyl phosphoric acid (**L14**) were also evaluated in this reaction, but led virtually to no reactivity (< 10% yield).

With optimized conditions in hand, we examined the scope of this β -C–H arylation protocol (Table 2). As expected, alcohols with primary β -C–H bonds exhibited high reactivity, leading to diarylation product along with

Table 2: Scope of aliphatic alcohols.^[a,b]

[a] Isolated yields. [b] The diastereomeric ratio was determined by ¹H NMR spectroscopy. [c] 1.3 equivalent of aryl iodide was used.

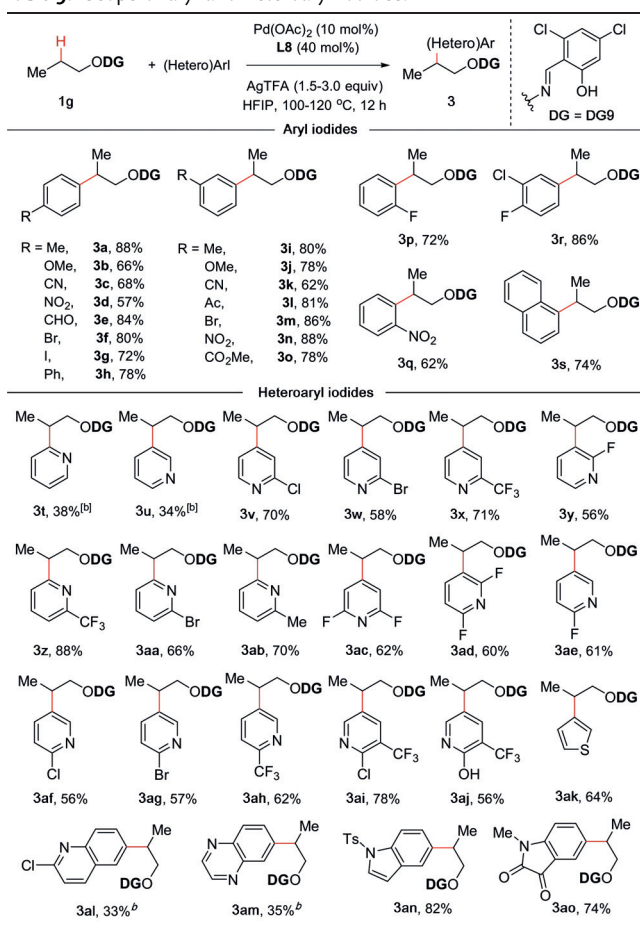
monoarylation product in most cases (**1a–1c**). Lower stoichiometry of aryl iodide was used in the cases of alcohols bearing multiple reactive sites in order to mitigate over-functionalization (**1d**, **1e**). Next, we set out to investigate the reactivity of secondary C–H bonds. We were pleased to find that, with our method, a series of linear primary alcohols exhibited very good reactivity and exclusive selectivity for the β-position (**1f–1h**, from 72 % to 85 % yield). Naturally occurring cetyl alcohol (**1k**) and lauryl alcohol (**1l**) also underwent arylation at the β-position in 71 % and 76 % yield, respectively. Benzylic (**1i**, 61 % yield) and homobenzylic (**1j**, 54 % yield) methylene C–H bonds proved less reactive, although affording product with high site-selectivity.

We next evaluated the compatibility of various functional groups with this transformation. Protected 1,3- and 1,4-amino alcohols (**1m**, **1n**), as well as substrates bearing acetoxy or carboxylate groups (**1o–1q**), led to good product yields (58–73 %). Interestingly, a free carboxylic acid was also compatible with the reaction (**1r**, 71 % yield). A series of tertiary amide substrates were tested under the same conditions, all of them giving moderate to good yields (48–62 %, **1s–1v**). Secondary alcohols with available β-methylene C–H bonds (**1w**, **1x**) also resulted in good yields, but with moderate diastereocontrol (d.r. = 4:1 and 5:1, respectively). Cyclobuta-

nol (**1y**) and cyclopentanol (**1z**) afforded the expected products in high yields (76 % and 82 %, respectively) and high selectivity for the *cis*-diastereomers. In contrast, medium-sized cycloalkanols such as cyclohexanol (**1aa**) and cycloheptanol (**1ab**) gave diastereomeric ratios of 1.5:1 and 2:1, respectively, although exhibiting excellent reactivity.

Having established the high efficiency of this protocol for the β-arylation of aliphatic alcohols, we turned our attention to aza-heterocycles, more challenging C–H activation substrates of potential interest in probe and drug development.^[16] We found that the choice of protecting group on the nitrogen atom was important for reactivity, with *N*-Cbz-protected and *N*-Ns-protected 3-hydroxy azetidine leading to no C–H activation product (**1ac**, **1ad**), while the corresponding *N*-trifluoroacetyl (*N*-TFA) resulted in 45 % yield (mono and di, **1ae**). Similarly, *N*-TFA 3-hydroxy-pyrrolidine (**1af**) and *N*-TFA 4-hydroxypiperidine (**1ag**) gave the expected arylation products in 42 % yield and 61 % yield (d.r. = 2:1), respectively. Finally, cyclopropyl methanol (**1ah**) was able to undergo C–H arylation at the β-site, a rare instance of palladium inserting into a tertiary C–H bond to form a quaternary carbon center.^[17]

Next, we examined the scope of aryl iodides as the coupling partner, using the propanol **DG9**-derivative as model substrate (Table 3). Both electron-donating and elec-

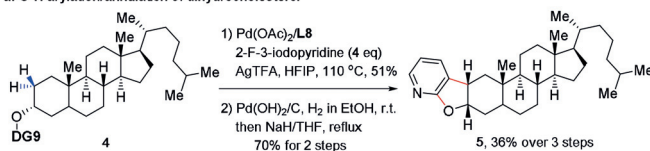
Table 3: Scope of aryl and heteroaryl iodides.^[a]

[a] Isolated yields. [b] The reaction was conducted at 120 °C.

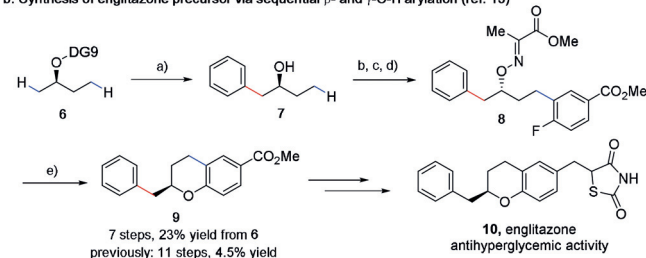
tron-withdrawing groups on the *para* or *meta* positions of aryl iodides ring resulted in good to excellent yields (**3a–3e**, **3h–3l**, **3n**, **3o**). Of note, products containing aryl bromide and aryl iodide functionality were readily accessed, (**3f**, **3g**, **3m**), offering the possibility for further diversification. In addition, *ortho*-substituted aryl iodides were also reactive with our method (**3p**, **3q**). Given the ubiquity of heteroaromatics in small-molecule drug discovery, we examined the reactivity of a wide range of aza-heteroaryl iodides. We were delighted to find that 2-substituted iodopyridines behaved well, leading to good to excellent product yields (**3v–3aj**). Unsubstituted iodopyridines also resulted in arylation product, albeit in moderate yield (**3t**, **3u**) presumably due to competitive coordination to the palladium catalyst. Other heteroaryl iodides such as iodothiophene, -quinoline, -quinoxaline, -indole and -oxindole were also suitable coupling partners (**3ak–3ao**), providing further support to the generality of this protocol.

To demonstrate the practical application of this method, we first turned to dihydrocholesterol as a substrate for C–H functionalization. Following directing group installation, a short sequence involving C–H arylation with 3-iodo-2-fluoropyridine, directing group removal and S_NAr cyclization generated a novel dihydrofuro[2,3-*b*]pyridine *cis*-fused structure (**5**, 36% yield from **4**, Scheme 2a). The new C–H functionalization protocol was further showcased in the synthesis of **9**, a known precursor of englitazone (of anti-hyperglycemic activity),^[18] via sequential β - and γ -C–H arylations. This route required a total of 7 transformations and proceeded in 23% yield, comparing favorably to the 11 steps and 4.5% overall yield previously reported (Scheme 2b).^[19]

a. C–H arylation/annulation of dihydrocholesterol



b. Synthesis of englitazone precursor via sequential β - and γ -C–H arylation (ref. 13)



Scheme 2. Practical application. Conditions: a) Substrate **6** (0.5 mmol), iodobenzene (0.6 mmol), Pd(OAc)₂ (10 mol%), **L8** (40 mol%), AgTFA (1.5 equiv), in HFIP (3.0 mL), 100 °C, 4 h; then Pd(OH)₂/C (20 mol%), H₂ (1 atm), in EtOH (2.0 mL), r.t., overnight, 65% yield over 2 steps; b) Ph₃P (1.2 equiv), NHPI (1.2 equiv), DIAD (1.5 equiv), in THF (2 mL), r.t., 95% yield; c) hydrazine monohydrate (2.0 equiv), in CH₂Cl₂/MeOH, 2 h, then pyruvic acid (5 equiv), 1 h, 95% yield; d) methyl 4-fluoro-3-iodobenzoate (1.5 equiv), Pd(OAc)₂ (10 mol%), **L8** (40 mol%), AgTFA (1.5 equiv), in HFIP (3.0 mL), 100 °C, 4 h; then SOCl₂/MeOH, 49% yield; e) Pd(OH)₂/C (20 mol%), H₂ (1 atm), in EtOH (2.0 mL), r.t., overnight; then NaH (3.0 equiv), in THF, 70 °C, overnight, 81% yield over 2 steps.

In summary, we have developed a protocol for the β -C(sp³)-H arylation of aliphatic alcohols. High yields and high degrees of β -specificity result from the combination of an electron-deficient 2-pyridone ligand and an L,X-type directing group that likely favors the formation of a [6,5]-fused palladacycle intermediate. This protocol, leading notably to the activation of methylene β -C–H bonds, is compatible with a wide range of substrates (including aza-heterocycles), and coupling partners (including heteroaryl iodides). Given the variety of commercially available aliphatic alcohol substrates and suitable coupling partners, we anticipate that this C(sp³)-H functionalization strategy will facilitate the synthesis of novel chemical matter, particularly in the context of drug discovery.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aliphatic alcohols · C–H activation · directing groups · ligands · synthetic methods

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