Pd^{II}-Catalyzed Site-selective β- and γ-C(sp^3)−H Arylation of Primary Aldehydes Controlled by Transient Directing Groups

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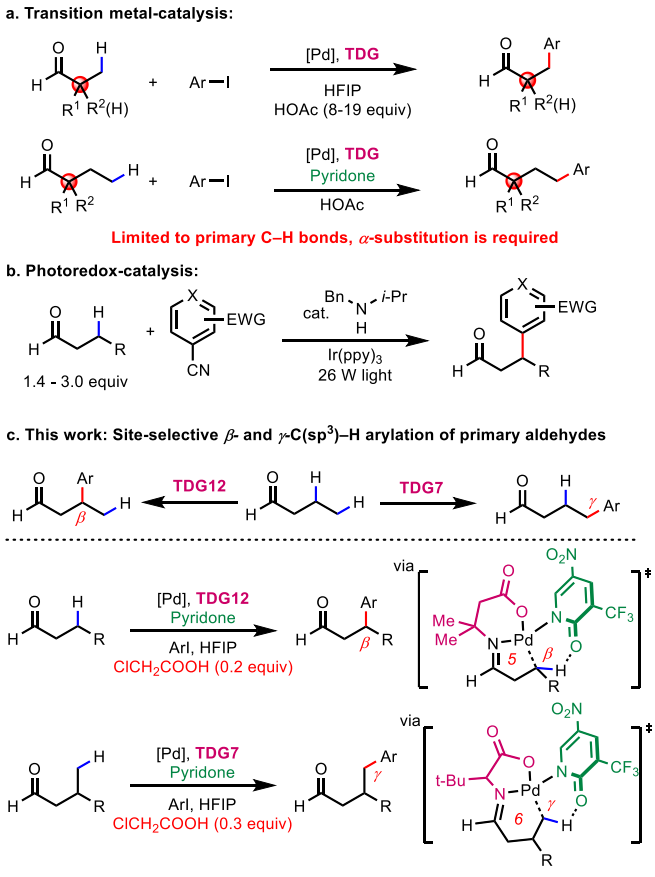
ABSTRACT: Pd(II)-catalyzed site-selective β- and γ-C(sp^3)−H arylation of primary aldehydes is developed by rational design of L,X-type transient directing groups (TDG). External 2-pyridone ligands are identified to be crucial for the observed reactivity. By minimizing the loading of acid additives, the ligand effect is enhanced to achieve high reactivities of the challenging primary aldehyde substrates. Site-selectivity can be switched from the proximate to the relatively remote position by changing the bite angle of TDG to match the desired palladacycle size. Experimental and computational investigations support this rationale for designing TDG to potentially achieve remote site-selective C(sp^3)−H functionalizations.

L,X-type transient directing groups (TDG) have emerged as a powerful tool in Pd(II)-catalyzed C–H functionalization since the first report in 2016.[1] Without the need of directing group installation and removal, the discovery and development of this class of TDG represents a significant advance for directed C–H activation reactions of ketones, aldehydes and amines that can form reversible imines with TDG.[2,3] Compared to ketone and amine substrates, C–H functionalizations of aldehydes are underdeveloped. Our initial report using glycine as a TDG for the C(sp^3)−H arylation was limited to ketones or o-tolualdehydes.[1] Subsequently, other benzylic and ortho-functionalizations of benzaldehyde derivatives have been extensively investigated.[4,5] Amino acid-based TDG has also been developed for aliphatic aldehydes by the Ge group and others to achieve β- and γ-arylation (**Scheme 1a**).[6] Despite these advances, substrates were limited to secondary or tertiary aldehydes. For primary aldehydes, only two individual examples have been reported to date by Li and Ge with 46% and 25% yield for methyl and methylene C(sp^3)–H arylation, respectively.[6a] In addition, β-methylene C−H functionalization of acyclic primary aldehydes remains to be developed.[6a,c,g] Most importantly, controlling site-selectivity in C(sp^3)–H activation by designing different TDG has not been demonstrated thus far. Notably, an alternative approach for β-arylation of aliphatic aldehydes have also been pursued via a radical pathway using cyanobenzene coupling partners and excess amount of aldehydes (**Scheme 1b**).[7]

Herein, we report a combination of ligand and TDG that enabled site-selective Pd^{II}-catalyzed C(sp^3)–H arylation of a broad range of primary aldehydes (**Scheme 1c**). With 3-amino-3-methylbutyric acid (**TDG12**) as transient directing group, β-methylene C–H arylation could be achieved with up to 83% yield. By simply employing a different **TDG7**, *tert*-Leucine, the regioselectivity could be switched to relative remote γ-position. Mechanistic studies combined with density functional theory （DFT） calculations suggested that matching the TDG bite angle with the size of palladacycle could minimize the strain in the C–H activation transition state (TS), thereby controlling the site-selectivity. Considering the recent extensive examples of remote C(sp^2)–H activation reactions developed using distance and geometry as the core parameters,[8] this finding represents a promising step towards systematical development of remote site-selective C(sp^3)–H activation.

Scheme 1. Direct C(sp^3)-H Arylation of Aliphatic Aldehydes



Scheme 2. Rational Design of Enhancing CMD Process

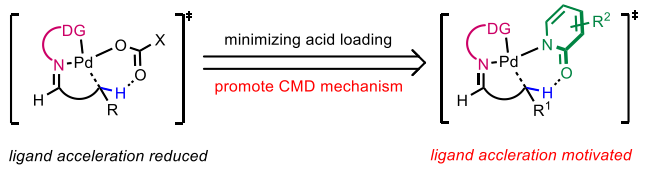
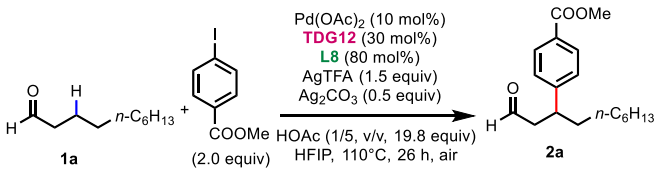
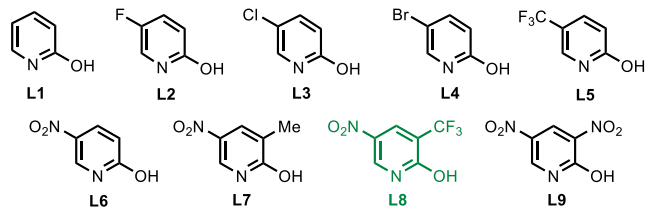


Table 1. Evaluation of Acids and Ligands[a, b]



Entry	Deviation from initial conditions	2a (%)
1	none	45 (52)[d]
2	HOAc (1/20, v/v, 5.7 equiv)	62 (72)[d]
3	HOAc (0.2 equiv)	54 (92)[d]
4	TFA (0.2 equiv) as acid[c]	57
5	$F_2CHCOOH$ (0.1 equiv) as acid[c]	53
6	Cl_3CCOOH (0.1 equiv) as acid[c]	36
7	**$ClCH_2COOH$ (0.2 equiv) as acid[c]**	**80** (96)[d]
8	No acid	46 (96)[d]
9	**L1** instead of **L8**, $ClCH_2COOH$ (0.2 equiv)	8
10	**L2** instead of **L8**, $ClCH_2COOH$ (0.2 equiv)	19
11	**L3** instead of **L8**, $ClCH_2COOH$ (0.2 equiv)	29
12	**L4** instead of **L8**, $ClCH_2COOH$ (0.2 equiv)	36
13	**L5** instead of **L8**, $ClCH_2COOH$ (0.2 equiv)	35
14	**L6** instead of **L8**, $ClCH_2COOH$ (0.2 equiv)	41
15	**L7** instead of **L8**, $ClCH_2COOH$ (0.2 equiv)	41
16	**L9** instead of **L8**, $ClCH_2COOH$ (0.2 equiv)	14
17	No Ligand, $ClCH_2COOH$ (0.2 equiv)	n.d.

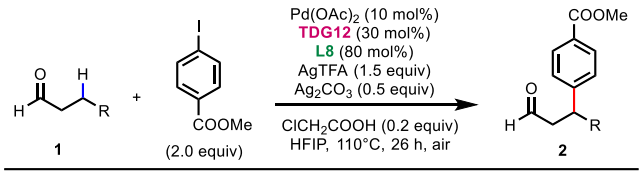


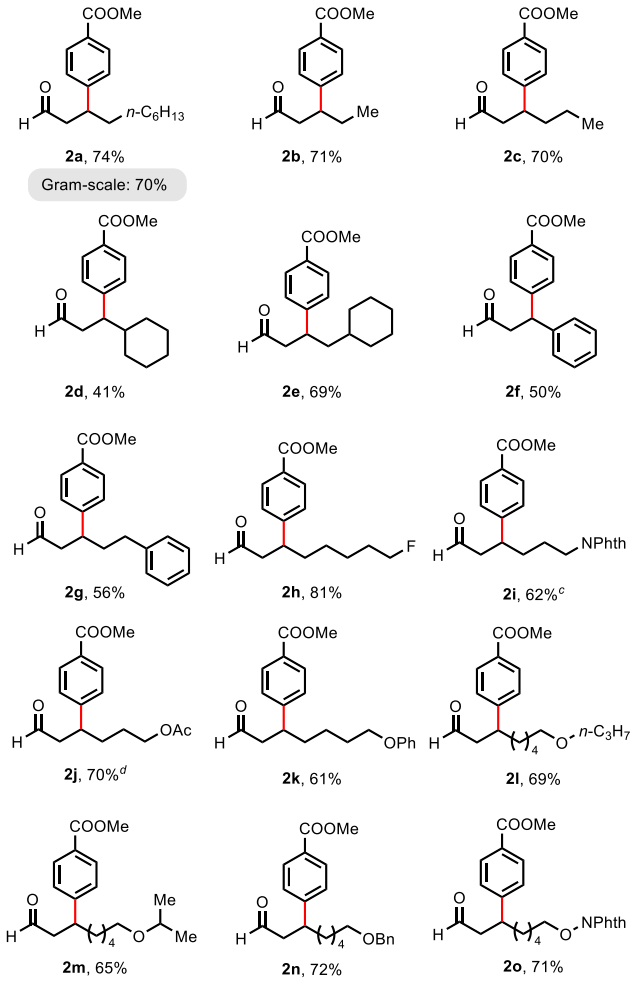
[a]Conditions: **1a** (0.1 mmol, 1.0 equiv), methyl 4-iodobenzoate (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **TDG12** (30 mol%), **ligand** (80 mol%), AgTFA (1.5 equiv), Ag_2CO_3 (0.5 equiv) and acid in HFIP (0.75 mL), 110°C, under air, 26 h. [b]Yield determined by ^1H NMR; CH_2Br_2 as internal standard. [c]Loading that gave the highest yield within a serial of concentrations. See SI for detailed screening. [d]Mass balance (combined yields of product and unreacted starting material).

To address the limitation of β- or γ-C–H functionalizations of aldehydes, we began to search for more effective ligands and TDG. Since the discovery of 2-pyridones as effective ligands for non-directed C–H activation of arenes,[9] this class of ligands has also found applications in several TDG-mediated sp^3 and sp^2 C–H activation reactions.[10] However, for TDG-mediated reactions, large excess of carboxylic acid is usually required to catalyze the attachment and dissociation of TDG, hence, the carboxylate could compete with pyridone for coordination and reduce the ligand acceleration effect (**Scheme 2**). Thus, we began to investigate the influence of the acid loading on the reaction.

In the mixture of HOAc/HFIP (1/5, v/v), model substrate decanal $Pd(OAc)_2$ (10 mol%), 3-amino-3-methylbutyric acid (**TDG12**, 30 mol%), 5-nitro-3-(trifluoromethyl)-2-pyridone (**L8**, 80 mol%), AgTFA (1.5 equiv) and Ag_2CO_3 (0.5 equiv) at 110 °C for 26 h. The reaction mixture was filtered through a short celite pad, followed by solvent removal to afford the β-C(sp^3)–H arylation product **2a** in 45% NMR yield (**Table 1**, entry 1). By lowering the acid loading

Table 2. Scope of Aldehydes for β-C(sp^3)–H Arylation[a, b]



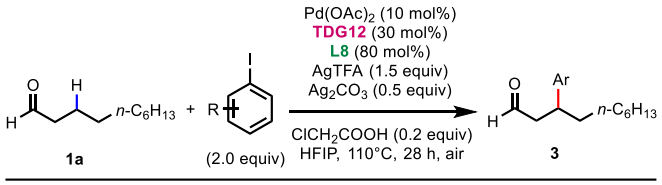


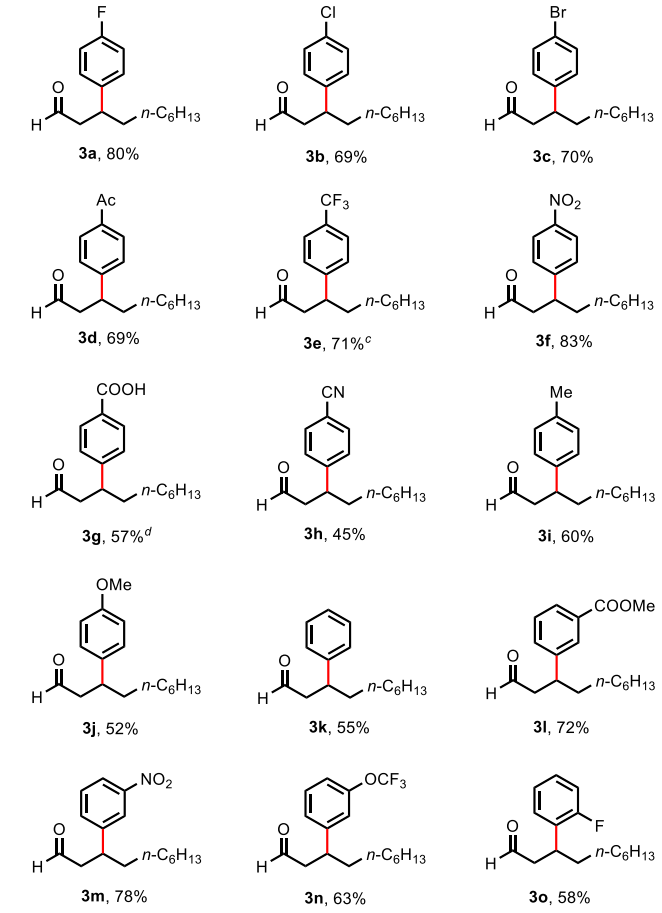
[a]Conditions: **1** (0.1 mmol, 1.0 equiv), methyl 4-iodobenzoate (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **TDG12** (30 mol%), **L8** (80 mol%), AgTFA (1.5 equiv), Ag_2CO_3 (0.5 equiv) and $ClCH_2COOH$ (0.2 equiv) in HFIP (0.75 mL), 110°C, under air, 26 h. [b]Isolated yields. [c]Reaction time 32 h. [d]Reaction time 72 h.

to 5.7 equiv, the reaction mass balance improved significantly from 52% to 72%. When minimal amount (0.2 equiv) of acid was used, 54% desired product was observed with mass balance reaching its highest at 92%. This observation is in line with our hypothesis that superstoichiometric amounts of carboxylates prevent ligand accelerated C–H activation and promote side reactions. Several other organic acids with lower pK_a were tested for their ability to promote the reversible imine formation with lower loading (entries 4-7). To our delight, replacing acetic acid with 0.2 equiv chloroacetic acid was found to be optimal, achieving 80% NMR yield of the product (entry 7). Notably, the reaction could occur without acid albeit with halved yield (entry 8). Presumably, the mild acidity of HFIP could catalyze the imine formation. Different

pyridone ligands were also evaluated for this reaction. Among unfunctionalized 2-pyridone (**L1**, entry 9) and 5-substituted 2-pyridones (**L2-L6**, entries 10-14), 5-nitro-2-pyridone (**L6**) gave the highest yield of 41%. Moreover, replacing the trifluoromethyl group (CF_3) at the 3-position of **L8** with a methyl or a nitro group (**L7** and **L9**) proved to be inefficient (entries 16-17). Not surprisingly, no arylation product was obtained in the absence of pyridone (entry 17).

Table 3. Scope of Aryl Iodide for β-C(sp^3)–H Arylation[a, b]

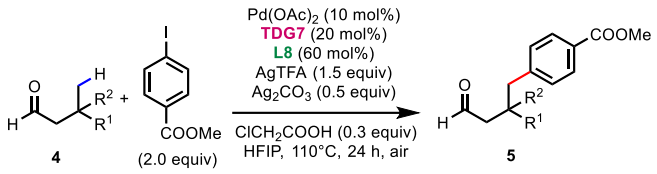


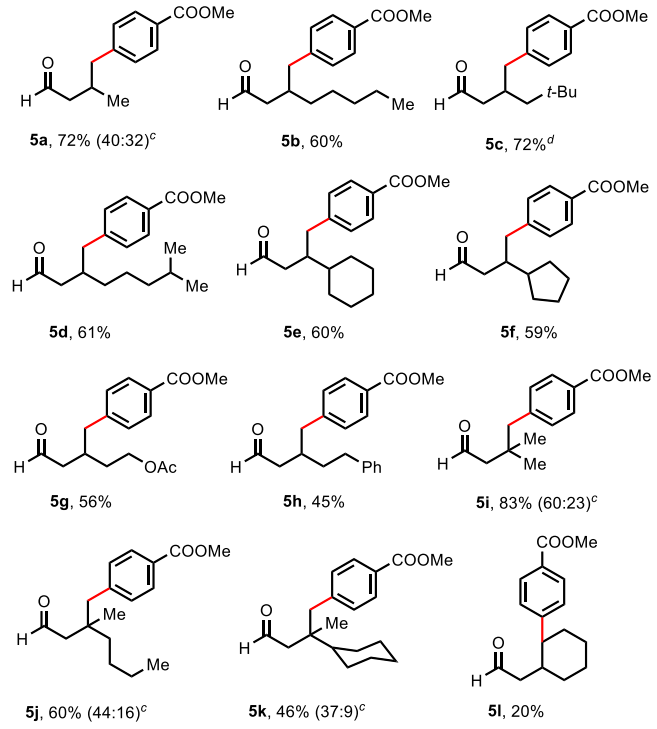


[a]Conditions: **1a** (0.1 mmol, 1.0 equiv), aryl iodide (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **TDG12** (30 mol%), **L8** (80 mol%), AgTFA (1.5 equiv), Ag_2CO_3 (0.5 equiv) and $ClCH_2COOH$ (0.2 equiv) in HFIP (0.75 mL), 110°C, under air, 28 h. [b]Isolated yields. [c]Reaction time 24 h. [d]Reaction time 36 h.

With the optimized conditions in hand, a variety of primary aldehydes with methylene β-C(sp^3)–H bonds were tested using methyl 4-iodobenzoate as the coupling partner (**Table 2**). Linear aldehydes were functionalized at the β-position to furnish **2a**-**2c** with good yields. Aldehyde bearing a large cyclohexyl group at the β-position showed inferior reactivity (**2d**, 41% yield), while cyclohexyl at the γ-position did not inhibit the reaction (**2e**). Arylation of benzylic β-C(sp^3)–H was also compatible, providing

Table 4. Scope of Aldehydes for γ-C(sp^3)–H Arylation[a, b]



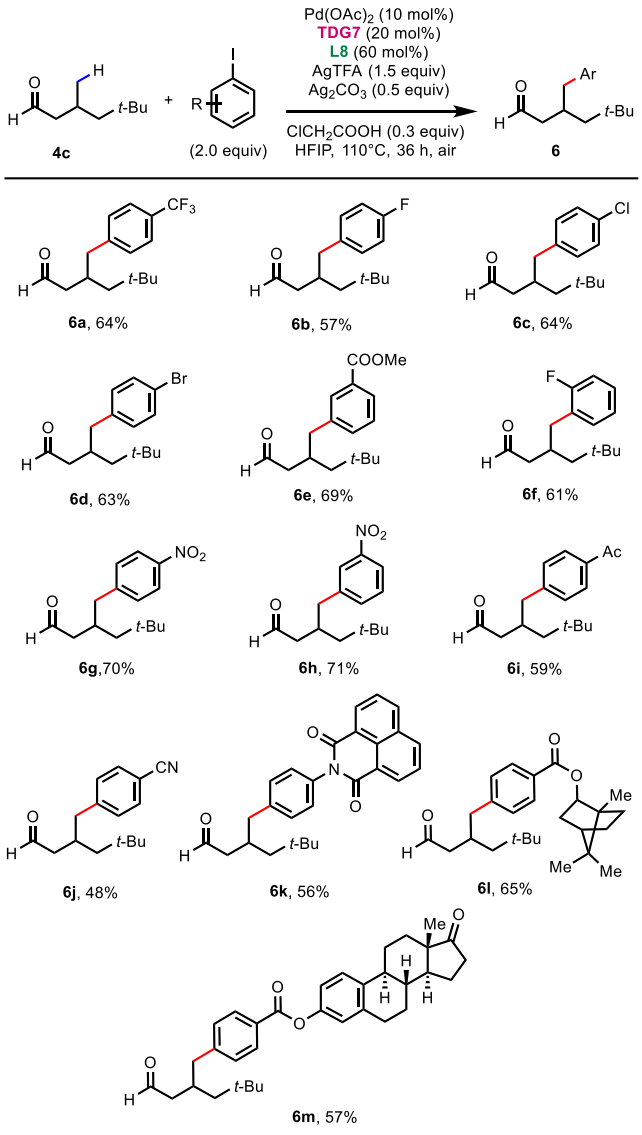


[a]Conditions: **4** (0.1 mmol, 1.0 equiv), methyl 4-iodobenzoate (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **TDG7** (20 mol%), **L8** (60 mol%), AgTFA (1.5 equiv), Ag_2CO_3 (0.5 equiv) and $ClCH_2COOH$ (0.3 equiv) in HFIP (0.50 mL), 110°C, under air, 24 h. [b]Isolated yields. [c]Ratio of mono: di. [d]Reaction time 36 h.

2f in a moderate yield. Substrates containing phenyl, fluoro, amide, acetate, ether, and *N*-oxyamide groups could all be functionalized with moderate to good yields (**2g**-**2o**). The reaction could be readily carried out in gram scale to provide **2a** in 70% yield (1.22g isolated).

Synthetic versatility of this reaction was further explored with the aryl iodide scope (**Table 3**). We selected the high boiling point decanal (**1a**) as the model substrate in order to readily determine mass balance and reaction time. The reaction was compatible with a broad scope of aryl iodides. Good to relatively high yields were acquired with para-substituted electron-deficient aryl iodides containing halogen, acetyl, trifluoromethyl and nitro groups (**3a**-**3f**). Surprisingly, the reaction also tolerated unprotected carboxylic acid functionality in the coupling partner to give **3g** in 57% yield with longer reaction time. However, the reaction with para-cyano-substituted aryl iodide resulted in **3h** with only 45% yield. The reactivities of electron-neutral iodides and iodides with election-donating groups were slightly lower, providing **3i**-**3k** in good to moderate yields. For other aryl iodides containing a meta- ester, nitro, and trifluoromethoxy group, good yields were also obtained (**3l**-**3n**). The ortho-fluoro-substituted aryl iodide showed moderate reactivity due to steric hindrance (**3o**).

Table 5. Scope of Aryl Iodide for γ-C(sp^3)−H Arylation[a, b]



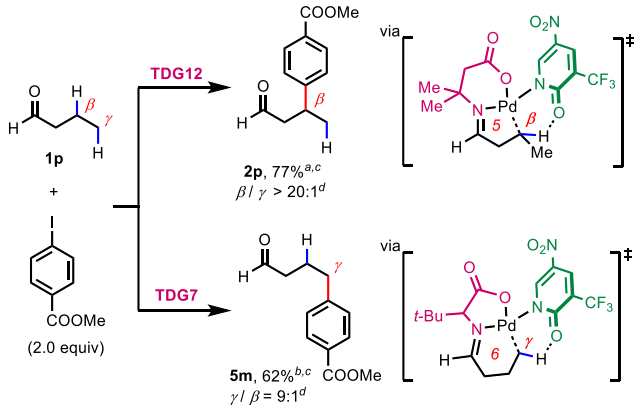
[a]Conditions: **4c** (0.1 mmol, 1.0 equiv), aryl iodide (2.0 equiv), Pd(OAc)$_2$ (10 mol%), **TDG7** (20 mol%), **L8** (60 mol%), AgTFA (1.5 equiv), Ag_2CO_3 (0.5 equiv) and $ClCH_2COOH$ (0.3 equiv) in HFIP (0.50 mL), 110°C, under air, 36 h. [b]Isolated yields.

When this β-methylene C−H arylation protocol was extended to γ-C−H arylation of aldehyde **4a**, less than 10% of the desired product was obtained. We wondered whether the six-membered cyclopalladation of the γ-C−H bond could be promoted by a TDG chelating with Pd(II) via 5-membered ring due to a better match of the bite angles. To our delight, *tert*-Leucine (**TDG7**) efficiently directed γ-C(sp^3)−H arylation of 3-methylbutanal, forming mono- and di-arylated products in 72% combined yield under slightly modified conditions. We then investigated other primary aldehydes to demonstrate the scope of compatible substrates (**Table 4**). The protocol tolerated a moderate to bulky substitution at the β-position. Substrates with pentyl, neopentyl, 4-methylpentyl, cyclohexyl or cyclopentyl groups could be transformed to the corresponding products in good yields (**5b-5f**). Acetoxy and phenyl groups were also shown to be compatible (**5g-5h**). Other primary aldehydes containing β-quaternary centers could be arylated at the γ-position efficiently, achieving good to moderate yields (**5i-5k**). At this stage, methylene γ-C(sp^3)−H arylation is less efficient, affording low yield (**5l**).

γ-C−H arylation reaction of **4c** with a plethora of aryl iodides exhibited a good functional-group compatibility (**Table 5**). Aryl iodides with various electron-withdrawing groups at the para, meta or ortho positions were coupled to the desired γ-C(sp^3)-H bonds in good yields (**6a-6f**). Coordinating groups such as nitro, acetyl, and cyano were also compatible (**6g-6j**). In addition, the reaction of fluorescent para-substituted *N*-(*p*-iodophenyl)-1,8-naphthalimide resulted in the fluorophore conjugate **6k** with 56% yield. Furthermore, aryl iodides derived from natural products such as estrone and borneol were also effectively functionalized to afford the desired products in 65% and 57% yields, respectively (**6l-6m**). However, electron-neutral and electron-rich aryl iodides exhibited poor reactivity, with 10-20% yields observed using 4-iodotoluene and 4-iodoanisole as coupling partners, for instance.

To further illustrate the impact of the chelating ring size of TDG on site-selectivity, we attempted the challenging site-selective C(sp^3)−H activation of a representative substrate containing both β-methylene and γ-primary C−H bonds (**Scheme 3**). To our delight, arylation of butanal **1p** afforded over 77% yield of the desired product (**2p**) with an exclusive β-selectivity (β/γ >20:1) when 6-membered chelating TDG (**TDG12**) was used. In contrast, the selectivity was switched to γ-arylation (γ/β=9:1) in 62% yield with 5-membered chelating TDG (**TDG7**). Considering that previously reported C(sp^3)−H activation reactions via a 6-membered palladacycle intermediate often needed substitutions at α/β positions to prevent β-C(sp^3)−H activation, the impact of the TDG on site-selectivity is significant.[11]

Scheme 3. Site-selective β- and γ-C(sp^3)−H Arylation

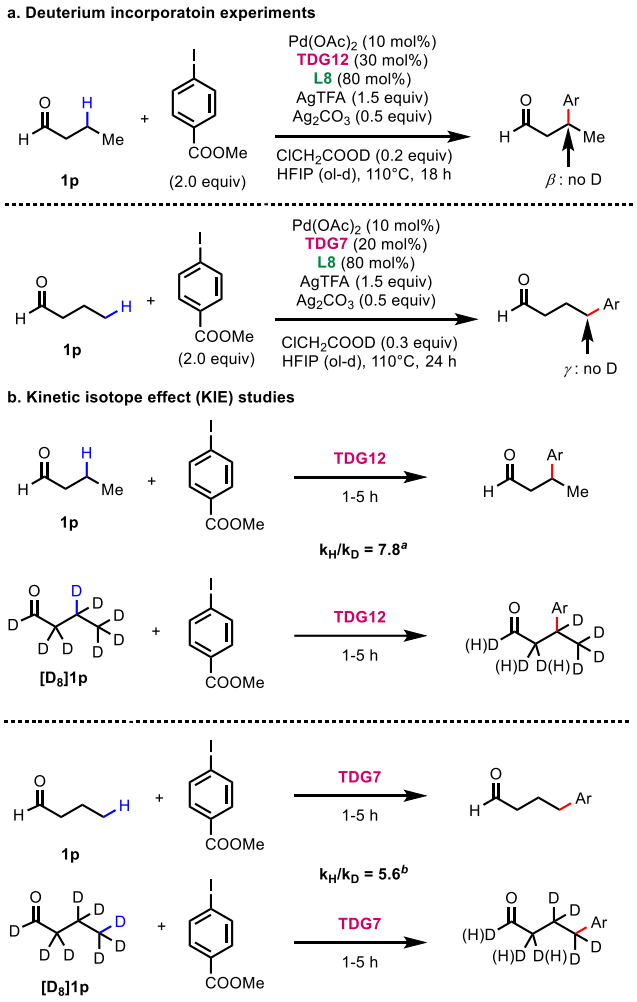


[a]Conditions: **1p** (0.1 mmol, 1.0 equiv), methyl 4-iodobenzoate (2.0 equiv), Pd(OAc)$_2$ (10 mol%), **TDG12** (30 mol%), **L8** (80 mol%), AgTFA (1.5 equiv), Ag_2CO_3 (0.5 equiv) and $ClCH_2COOH$ (0.2 equiv) in HFIP (0.75 mL), 110°C, under air, 18 h. [b]Conditions: **1p** (0.1 mmol, 1.0 equiv), methyl 4-iodobenzoate (2.0 equiv), Pd(OAc)$_2$ (10 mol%), **TDG7** (20 mol%), **L8** (80 mol%), AgTFA (1.5 equiv), Ag_2CO_3 (0.5 equiv) and $ClCH_2COOH$ (0.3 equiv) in HFIP (0.65 mL), 110°C, under air, 24 h. [c]Isolated yields. [d]ratio determined by ^{1}H NMR of the crude mixture.

Although we have reported a single example of controlling γ/β selectivity in directed C(sp^3)−H arylation of alcohols by designing different covalent L,X-type directing groups, the origin of the selectivity has not been investigated in-depth.[12,13] The β-site-selectivity using amino acid-based TDG for C(sp^3)−H activation of ketones has been rationalized through computational studies.[14] This first example of TDG-controlled β- and γ-C(sp^3)−H activation offers us a unique opportunity to probe the origin of site-selectivity.

We hence performed deuterium incorporation experiments in the presence of 2-chloroacetic acid-d and HFIP-ol-D (**Scheme 4a**). The absence of deuterium incorporation in the arylated products suggested that the C−H cleavage step was irreversible for both *β*- and *γ*-C(sp^3)−H arylation. Moreover, kinetic isotope effect (KIE) studies revealed large primary KIE values (KIE$_\beta$ of 7.8 and KIE$_\gamma$ of 5.6) when using *β*- and *γ*-deuterated substrates (**Scheme 4b**). These results are consistent with the C−H cleavage being the rate- and site-selectivity-determining step for both *β*- and *γ*-C(sp^3)−H arylation.

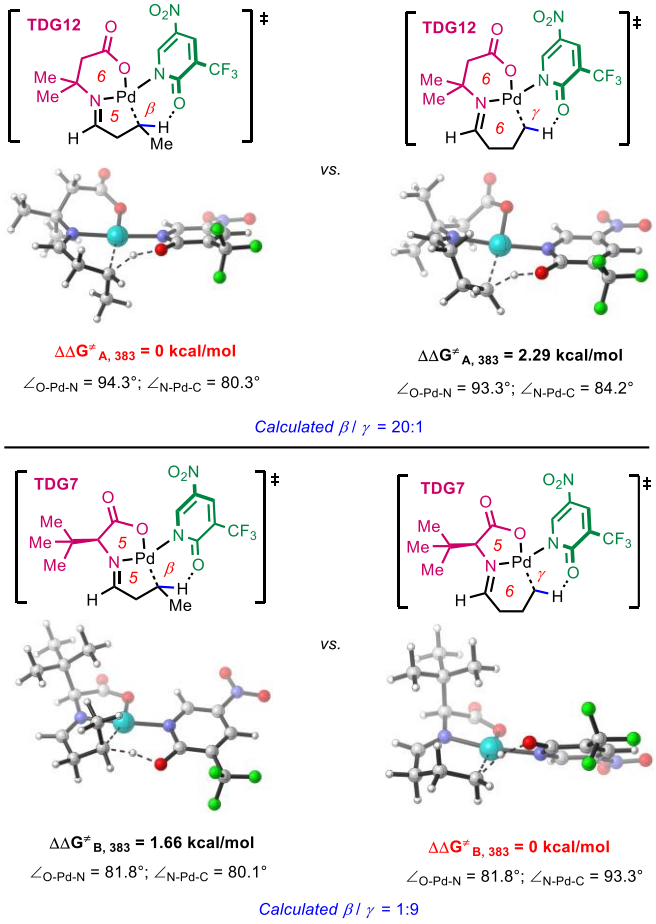
Scheme 4. Mechanistic Studies



[a]Conditions: **1p** (0.1 mmol, 1.0 equiv), methyl 4-iodobenzoate (2.0 equiv), Pd(OAc)$_2$ (10 mol%), **TDG12** (30 mol%), **L8** (80 mol%), AgTFA (1.5 equiv), Ag_2CO_3 (0.5 equiv) and $ClCH_2COOH$ (0.2 equiv) in HFIP (0.75 mL), 110°C, under air, 1-5 h. [b]Conditions: **1p** (0.1 mmol, 1.0 equiv), methyl 4-iodobenzoate (2.0 equiv), Pd(OAc)$_2$ (10 mol%), **TDG7** (20 mol%), **L8** (80 mol%), AgTFA (1.5 equiv), Ag_2CO_3 (0.5 equiv) and $ClCH_2COOH$ (0.3 equiv) in HFIP (0.65 mL), 110°C, under air, 1-5 h.

With these findings in hand, we began to investigate the influence of TDG on site-selectivity by DFT modeling of the corresponding C−H cleavage transition states (TS). We used **1p** as the model substrate for our studies (please see the SI for computational details). With **L8** as the ligand, 4 ensembles of TS were located, corresponding to *β*- and *γ*-C(sp^3)−H activation with **TDG12** and **TDG7** (**Scheme 5**, lowest TS shown). Calculated *β*/*γ*-site-selectivity and relative activation free energies ($\Delta\Delta G^{\neq}_{383}$) were obtained from the ratios of combined Boltzmann populations of the corresponding TS ensembles. *β*-C(sp^3)−H activation was calculated to be favored over *γ*- by 2.29 kcal/mol with **TDG12**, while with **TDG7** the selectivity was reversed with a free energy difference of 1.66 kcal/mol. These values correspond to 20:1 and 1:9 calculated *β*/*γ*- ratios, respectively, in excellent agreement with the experimental observations (**Scheme 3**). Our studies suggest that the site-selectivity of C−H cleavage is controlled by the bite angle of the TDG. Evidently, the 5,6-membered coordination (with O−Pd−C angle of around 175°) is preferred over the 5,5- or 6,6-membered coordination, where additional ring strain in the C−H cleavage TS renders them less favored. This finding is also consistent with the ring strain of fused carbocyclic rings.[15]

Scheme 5. DFT Modeling of The TDG Influence on Site-selectivity of C(sp^3)−H Cleavage[a]



[a]The lowest TS for each TS ensemble is shown. Calculated ratios and relative free energies were obtained from Boltzmann populations of the TS in the corresponding ensembles at 383 K. Please see the SI for computational details.

In summary, we have developed a protocol for Pd^{II}-catalyzed site-selective *β*-methylene and *γ*-C(sp^3)−H arylation of primary aldehydes. This reaction features broad substrate scope with good functional group compatibility, exemplified by successful C–H arylation of a range of readily oxidizable aldehydes under mild conditions. Moreover, this strategy highlighted the influence of TDG on site-selectivity through matching the bite angles between the palladacycle and the TDG chelation, providing a guidance for

the future design of ligands or TDG. Efforts to develop TDG to achieve γ-methylene C−H activation using this principle are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at

Full experimental details, mechanistic studies, computational studies and characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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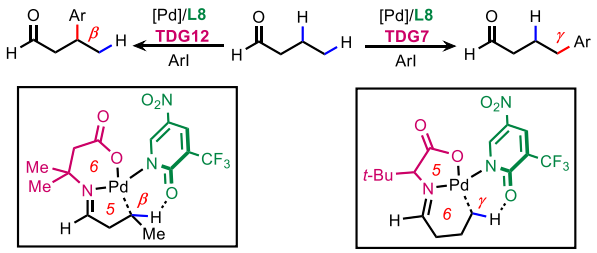
[Pd]/L8
TDG12
ArI
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TDG7
ArI
Ar
β
γ
5-Membered Palladacycle
6-Membered Palladacycle