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Palladium-Catalyzed Site-Selective C(sp^3)−H Arylation of Phenylacetaldehydes

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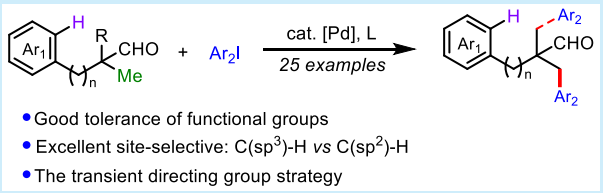
Supporting Information

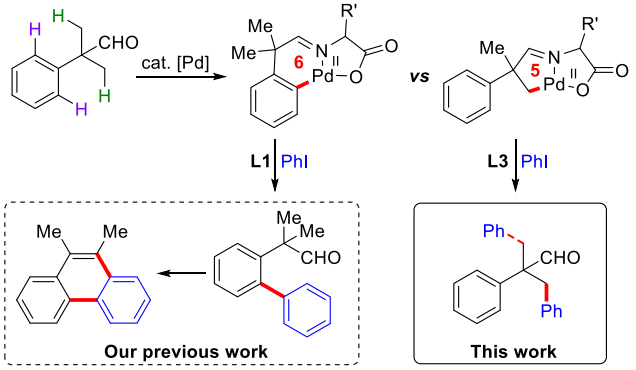
ABSTRACT: We describe a Pd-catalyzed selective C−H arylation reaction of phenylacetaldehydes using L-valine as the transient directing group. This process showed a broad substrate scope and excellent selectivity in which a ligand-controlled functionalization of the unactivated β-C(sp^3)−H bond. In addition, enantioselective arylation of phenylacetaldehydes was preliminarily explored by utilizing a bulky chiral transient directing group.



Palladium-catalyzed C−H activations is a powerful vehicle for C−C and C−X (heteroatom) bond formation during the past decades.[1] Substrates that contain an auxiliary directing group have been broadly exploited in selective C−H bond activation reactions,[1,2] although preinstalling directing groups on substrates reduce the overall efficiency. Recently, the transient directing group has emerged as a hot topic in the field of C−H bond activations[3] because a reversible intermediate such as imine could be formed between a substrate and a ligand, simplifying the manipulation steps of traditional C−H bond activations.[4,5] Many remarkable endeavors have been made to develop transient directing group strategy in C−H bonds activations.[3−5] Generally, C(sp^2)−H bond activation is prior than that of C(sp^3)−H bonds in such metal-catalyzed reactions.[6] Many published examples report functionalization of C(sp^2 or sp^3)−H bonds separately in different substrates.[7] Studies on the selective C(sp^2 or sp^3)−H bond activation in one molecule remains a challenge.[8]

Recently, we reported a glycine assisted C(sp^2)−H arylation and in situ tandem reaction of phenylacetaldehydes, a variety of functionalized phenanthrenes were prepared with a satisfactory results (Scheme 1).[9] On the basis of our and other groups' work, we envisioned that the β-C(sp^3)−H arylation of phenylacetaldehydes with aryl iodides would be realized utilizing a similar strategy. We describe herein a new protocol for the highly site-selective C(sp^3)−H bonds activation in one molecule under the assistance of a transient directing group, delivering aldehydes with a homobenzylic (stereo)centers (Scheme 1), which are highly prevalent in natural products and medicinally relevant compounds.[10] The principal challenges of this approach arise from (1) the need to find appropriate reaction conditions to efficiently avoid the generation of a six-membered palladacycle[11] and (2) selective C(sp^3)−H bonds activation to give β-mono- or β,β'-diarylation products.

Scheme 1. Pd-Catalyzed Selective C−H Activation



We initiated to evaluate the palladium(II)-catalyzed cross coupling reaction of 2-methyl-2-phenylpropanal (**1a**) and iodobenzene (**2a**) in a cosolvent (hexafluoroisopropanol (HFIP)/AcOH, 1/1) under a nitrogen atmosphere at 125 °C for 12 h in the presence of glycine (**L1**) as the ligand and AgTFA as the additive (Table 1). Encouragingly, the expected arylated product **3a** and a small amount of diarylation product **3a′** (3%) were isolated, together with a C(sp^2)−H activation and cyclization product phenanthrene **4a** in 27% yield. To increase the reactivity and site selectivity of this conversion, various ligands (**L1**−**L8**) were screened (entries 2−8). A significantly increase in this reaction was realized with substituted 2-aminopropanoic acids **L2**−**L4** as the ligands (entries 2−4), the yield of **3** was improved (61%, mono/di = 50:11) with the C(sp^2)−H arylation completely prevented by using **L3** as the transient directing group (entry 3). Obviously, α-substituted amino acids returned good selectivity of C(sp^3)−

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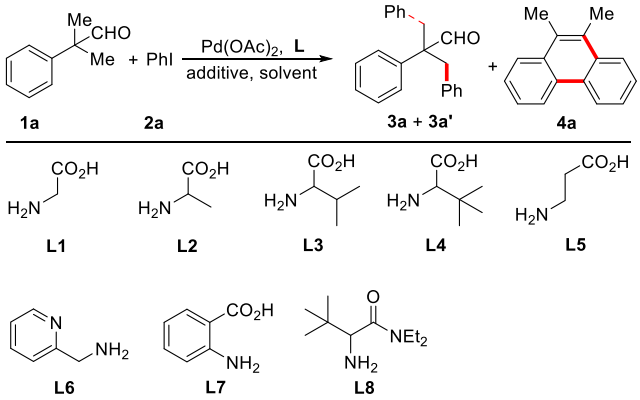
Table 1. Optimization of the Reaction Conditions[a]



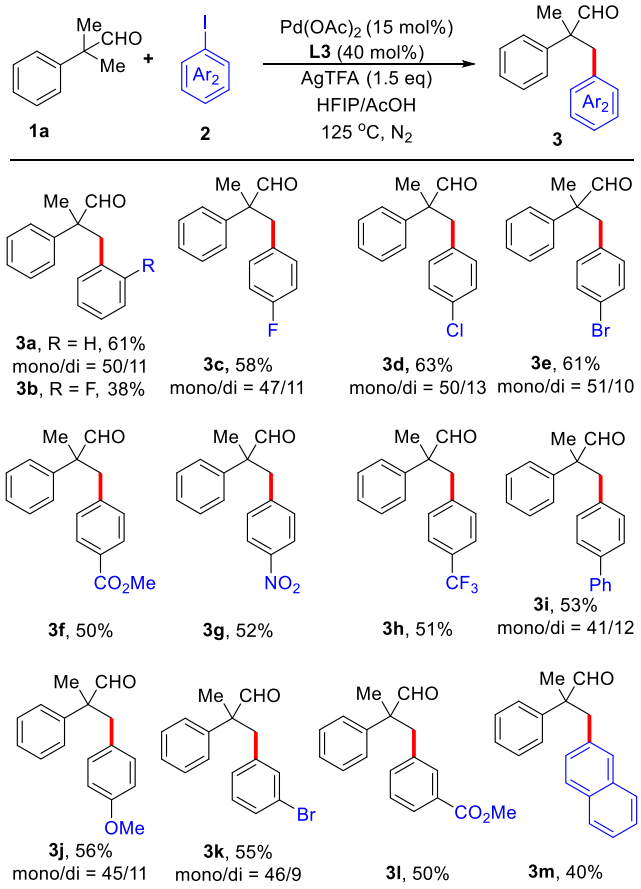
entry	solvent	ligand	additive	yield[b] 3a	3a′	4a
1	HFIP/AcOH (1/1)	**L1**	AgTFA	18	3	27
2	HFIP/AcOH (1/1)	**L2**	AgTFA	39	8	8
3	HFIP/AcOH (1/1)	**L3**	AgTFA	50	11	
4	HFIP/AcOH (1/1)	**L4**	AgTFA	46	7	
5	HFIP/AcOH (1/1)	**L5**	AgTFA	19	22	5
6	HFIP/AcOH (1/1)	**L6**	AgTFA			
7	HFIP/AcOH (1/1)	**L7**	AgTFA	6		
8	HFIP/AcOH (1/1)	**L8**	AgTFA	3		
9	HFIP/AcOH (1/1)		AgTFA			
10	HFIP/AcOH (3/1)	**L3**	AgTFA	42	6	5
11	HFIP/AcOH (1/3)	**L3**	AgTFA	43	4	
12[c]	HFIP/AcOH (1/1)	**L3**	AgTFA	46	6	trace
13[d]	HFIP/AcOH (1/1)	**L3**	AgTFA	28	3	
14[e]	HFIP/AcOH (1/1)	**L3**	AgTFA	24	trace	
15[f]	HFIP/AcOH (1/1)	**L3**	AgTFA	18	trace	
16	HFIP/AcOH (1/1)	**L3**	AgOAc	30	4	
17	HFIP/AcOH (1/1)	**L3**	Ag_2CO_3	19	trace	
18	HFIP/AcOH (1/1)	**L3**	Ag_2O	15		

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Pd source (0.03 mmol), **L** (0.08 mmol), additive (0.3 mmol), solvent (1.0 mL), N_2, 125 °C, 12 h. [b]Isolated yields. [c]$Pd(TFA)_2$ as Pd source. [d]$Pd(PPh_3)_2Cl_2$ as Pd source. [e]$[PdCl(\eta^3\text{-}C_3H_5)]_2$ as Pd source. [f]$PdCl_2$ as Pd source.

H arylation, suggesting that the formation of the 5-membered palladacycle is strengthened by the larger substituents of α-amino acids, probably due to the Thorpe−Ingold effect (entries 1 vs 2−4). 3-Aminopropanoic acid (**L5**) was also tested and afforded poor selectivity (entry 5). No reaction was detected when **L6** was used (entry 6). Further screening of ligand with either **L7** or **L8** afforded an inferior result (entries 7 and 8). A control experiment indicated that the transient directing group was absolutely critical in this approach (entry 9). Then various palladium catalysts were conducted, but all returned low yields (entries 12−15). Besides AgTFA, we further used AgOAc, Ag_2CO_3, and Ag_2O as silver salts, and the desired product **3** also could be obtained with inferior reaction performance (entries 16−18).

In order to gauge the scope and generality of the newly established method, a series of structurally diverse aryl iodides were tested under the optimal reaction conditions. The results are shown in Scheme 2, where aryl iodides containing an electron-donating group (**3j**) or electron-withdrawing groups (**3f−h**, **3l**) were well accommodated. Meanwhile, aryl iodides with the substituents F, Cl, and Br at the para, meta, or ortho position all proceeded smoothly with moderate yields and thus enabled further transformations of products via cross-coupling reactions (**3b−3e**, **3k**). Besides, **3m** was also obtained when 2-iodonaphthalene was employed. Generally, mixed products of mono and diarylation were detected in this process. Interestingly, methyl 4-iodobenzoate, 4-nitroiodobenzene, 4-(trifluoromethyl)iodobenzene, and methyl 3-iodobenzoate bearing strong electron-withdrawing groups or naphthyl returned only monoarylation products (**3f−3h, 3l**, and **3m**). All of the reactions showed excellent site selectivity with moderate to good reactivity. Nonetheless, the heterocyclic aryl iodines such as 3-iodopyridine and 2,6-dichloro-4-iodopyridine gave no desired products.

Scheme 2. Scope of Aryl Iodides[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (0.03 mmol), **L3** (0.08 mmol), AgTFA (0.32 mmol), [HFIP/AcOH (1/1, v/v) 1.0 mL], 12 h, N_2. Isolated yields.

Afterward, we proceeded to explore the scope with regard to the various substituted aldehydes by using a coupling partner **2f**. As shown in Scheme 3, ortho-, meta-, and para substitutions as well as disubstituted methylenedioxy and naphthyl are also well tolerated in this reaction (**3n−3w**). Aldehyde bearing an ethyl at the α-position was also suitable substrates for the catalytic process to yield the desired product **3x**. Remarkably, arylation occurred only at the methyl group, and no benzylic methylene product was detected under these conditions (**3y**). Notably, no diarylation products were observed in these reactions. Unfortunately, nonquaternary carbon aldehydes such as 2-phenylpropanal and 2-methylpentanal returned no desired product.

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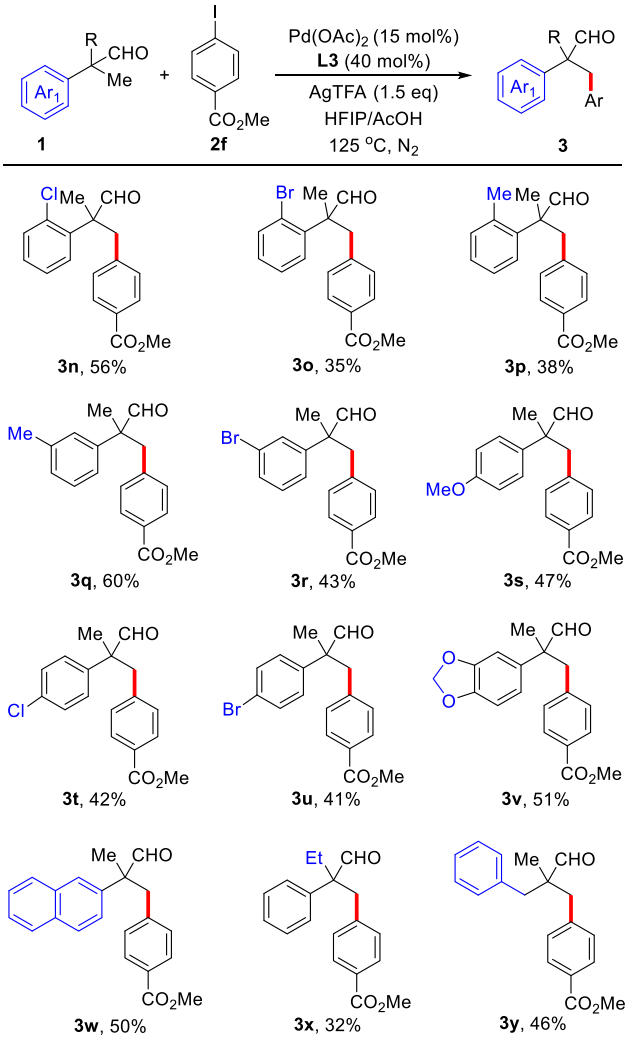
Scheme 3. Scope of Aldehydes[a]

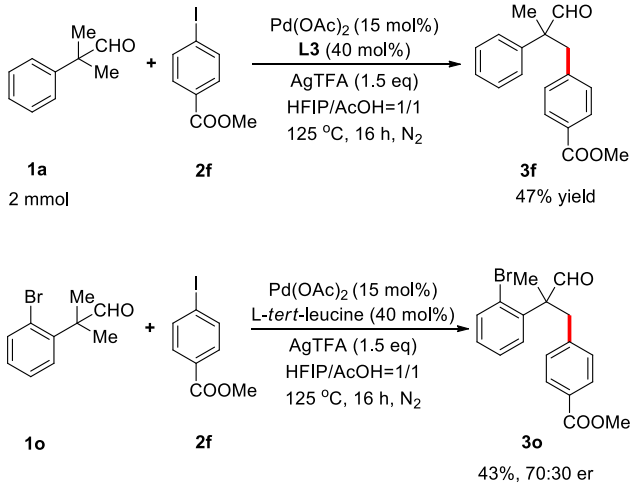


[a]Reaction conditions: **1** (0.2 mmol), **2f** (0.4 mmol), $Pd(OAc)_2$ (0.03 mmol), **L3** (0.08 mmol), AgTFA (0.3 mmol), [HFIP/AcOH (1/1, v/v) 1.0 mL], 12 h, N_2. Isolated yields.

To demonstrate the potential application of this newly developed protocol, a scaled-up experiment using **1a** with methyl 4-iodobenzoate was conducted (Scheme 4). As a result, arylated product **3f** could be prepared in 47% yield under similar conditions. Application of this strategy to the enantioselective arylation of **1o** was then examined, and the reaction proceeded successfully with L-*tert*-leucine and produced the corresponding product **3o** (43%) with a promising enantiomeric ratio (er) of 70:30 (Scheme 4). Unfortunately, a detailed screening of a range of chiral amino acids (**C1**−**C10**) and substrates returned no further improvement of the enantioselectivity (see the SI for details).

In conclusion, we have achieved a palladium-catalyzed highly site-selective C(sp^3)−H arylation reaction of phenylacetaldehydes with aryl iodides by using a easily available transient directing group. Attractive features of this method include broad substrate scope and excellent regioselectivity, wherein the functionalization of benzylic methylene or γ-C(sp^2)−H bonds could be effectively avoided. The detailed mechanistic studies and further efforts to improve enantioselectivity with this reaction using novel chiral amino acids are underway.

Scheme 4. Scale up Reaction and Exploration of Enantioselective Arylation



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02650.

Experimental procedures, characterization data for all new compounds, and copies of ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. Transition-Metal-Catalyzed Direct Arylation of (Hetero)Arenes by C−H Bond Cleavage. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792−9826. (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. Palladium- and Copper-Catalyzed Arylation of Carbon−Hydrogen Bonds. *Acc. Chem. Res.* **2009**, *42*, 1074−1086. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Palladium(II)-Catalyzed C−H Activation/C−C Cross-Coupling Reactions: Versatility and Practicality. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115. (d) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. Functionalization of Organic Molecules by Transition-

DOI: 10.1021/acs.orglett.9b02650
Org. Lett. XXXX, XXX, XXX−XXX

Metal-Catalyzed C(sp^3)−H Activation. *Chem. - Eur. J.* **2010**, *16*, 2654−2672. (e) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C−H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147−1169. (f) Baudoin, O. Transition metal-catalyzed arylation of unactivated C(sp^3)−H bonds. *Chem. Soc. Rev.* **2011**, *40*, 4902−4911. (g) Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. C−H Functionalization in organic synthesis. *Chem. Soc. Rev.* **2011**, *40*, 1855−1856. (h) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. Towards mild metal-catalyzed C−H bond activation. *Chem. Soc. Rev.* **2011**, *40*, 4740−4761. (i) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. Beyond Directing Groups: Transition-Metal-Catalyzed C−H Activation of Simple Arenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236−10254. (j) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. C−H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960−9009. (k) Li, B.-J.; Shi, Z.-J. From C(sp^2)−H to C(sp^3)−H: systematic studies on transition metal-catalyzed oxidative C−C formation. *Chem. Soc. Rev.* **2012**, *41*, 5588−5598. (l) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. Transition metal-catalyzed ketone-directed or mediated C−H functionalization. *Chem. Soc. Rev.* **2015**, *44*, 7764−7786. (m) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. Palladium-Catalyzed Transformations of Alkyl C−H Bonds. *Chem. Rev.* **2017**, *117*, 8754−8786. (n) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. Catalytic Enantioselective Transformations Involving C−H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev.* **2017**, *117*, 8908−8976.

(2) (a) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C−H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *111*, 1315−1345. (b) Rouquet, G.; Chatani, N. Catalytic Functionalization of C(sp^2)−H and C(sp^3)−H Bonds by Using Bidentate Directing Groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726−11743. (c) Daugulis, O.; Roane, J.; Tran, L. D. Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon-Hydrogen Bonds. *Acc. Chem. Res.* **2015**, *48*, 1053−1064. (d) He, G.; Wang, B.; Nack, W. A.; Chen, G. Syntheses and Transformations of α-Amino Acids via Palladium-Catalyzed Auxiliary-Directed sp^3 C−H Functionalization. *Acc. Chem. Res.* **2016**, *49*, 635−645.

(3) (a) Park, Y. J.; Park, J.-W.; Jun, C.-H. Metal-Organic Cooperative Catalysis in C−H and C−C Bond Activation and Its Concurrent Recovery. *Acc. Chem. Res.* **2008**, *41*, 222−234. (b) Rousseau, G.; Breit, B. Removable Directing Groups in Organic Synthesis and Catalysis. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450−2494. (c) Jun, C.-H.; Lee, H.; Hong, J.-B. Chelation-Assisted Intermolecular Hydroacylation: Direct Synthesis of Ketone from Aldehyde and 1-Alkene. *J. Org. Chem.* **1997**, *62*, 1200−1201. (d) Yeung, C. S.; Dong, V. M. A New Direction in Enantioselective Catalysis: Scaffolding Ligands in Olefin Hydroformylation. *Angew. Chem., Int. Ed.* **2011**, *50*, 809−812. (e) Jun, C.-H.; Chung, K.-Y.; Hong, J.-B. C−H and C−C Bond Activation of Primary Amines through Dehydrogenation and Transimination. *Org. Lett.* **2001**, *3*, 785−787. (f) Tan, P. W.; Juwaini, N. A. B.; Seayad, J. Rhodium(III)-Amine Dual Catalysis for the Oxidative Coupling of Aldehydes by Directed C−H Activation: Synthesis of Phthalides. *Org. Lett.* **2013**, *15*, 5166−5169. (g) Grünanger, C. U.; Breit, B. Branched-Regioselective Hydroformylation with Catalytic Amounts of a Reversibly Bound Directing Group. *Angew. Chem., Int. Ed.* **2008**, *47*, 7346−7349. (h) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. Catalytic Scaffolding Ligands: An Efficient Strategy for Directing Reactions. *J. Am. Chem. Soc.* **2008**, *130*, 9210−9211. (i) Grünanger, C. U.; Breit, B. Remote Control of Regio- and Diastereoselectivity in the Hydroformylation of Bishomoallylic Alcohols with Catalytic Amounts of a Reversibly Bound Directing Group. *Angew. Chem., Int. Ed.* **2010**, *49*, 967−970. (j) Mo, F.; Dong, G. Regioselective ketone α-alkylation with simple olefins via dual activation. *Science* **2014**, *345*, 68−72.

(4) For selected examples, see: (a) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. Functionalization of C(sp^3)−H bonds using a transient directing group. *Science* **2016**, *351*, 252−256. (b) Ma, F.; Lei, M.; Hu, L. Acetohydrazone: A Transient Directing Group for Arylation of Unactivated C(sp^3)−H Bonds. *Org. Lett.* **2016**, *18*, 2708−2711. (c) Yang, K.; Li, Q.; Liu, Y.; Li, G.; Ge, H. Catalytic C−H Arylation of Aliphatic Aldehydes Enabled by a Transient Ligand. *J. Am. Chem. Soc.* **2016**, *138*, 12775−12778. (d) Hong, K.; Park, H.; Yu, J.-Q. Methylene C(sp^3)−H Arylation of Aliphatic Ketones Using a Transient Directing Group. *ACS Catal.* **2017**, *7*, 6938−6941. (e) Chen, X.-Y.; Ozturk, S.; Sorensen, E. J. Pd-Catalyzed Ortho C−H Hydroxylation of Benzaldehydes Using a Transient Directing Group. *Org. Lett.* **2017**, *19*, 6280−6283. (f) Chen, X.-Y.; Ozturk, S.; Sorensen, E. J. Synthesis of Fluorenones from Benzaldehydes and Aryl Iodides: Dual C−H Functionalizations Using a Transient Directing Group. *Org. Lett.* **2017**, *19*, 1140−1143. (g) Liu, X.-H.; Park, H.; Hu, J.-H.; Hu, Y.; Zhang, Q.-L.; Wang, B.-L.; Sun, B.; Yeung, K.-S.; Zhang, F.-L.; Yu, J.-Q. Diverse ortho-C(sp^2)−H Functionalization of Benzaldehydes Using Transient Directing Groups. *J. Am. Chem. Soc.* **2017**, *139*, 888−896. (h) Yao, Q.-J.; Zhang, S.; Zhan, B.-B.; Shi, B.-F. Atroposelective Synthesis of Axially Chiral Biaryls by Palladium-Catalyzed Asymmetric C−H Olefination Enabled by a Transient Chiral Auxiliary. *Angew. Chem., Int. Ed.* **2017**, *56*, 6617−6621. (i) Xu, J.; Liu, Y.; Wang, Y.; Li, Y.; Xu, X.; Jin, Z. Pd-Catalyzed Direct ortho-C−H Arylation of Aromatic Ketones Enabled by a Transient Directing Group. *Org. Lett.* **2017**, *19*, 1562−1565. (j) St John-Campbell, S.; White, A. J. P.; Bull, J. A. Single operation palladium catalysed C(sp^3)−H functionalisation of tertiary aldehydes: investigations into transient imine directing groups. *Chem. Sci.* **2017**, *8*, 4840−4847. (k) Liao, G.; Yao, Q.-J.; Zhang, Z.-Z.; Wu, Y.-J.; Huang, D.-Y.; Shi, B.-F. Scalable, Stereocontrolled Formal Syntheses of (+)-Isoschizandrin and (+)-Steganone: Development and Applications of Palladium(II)-Catalyzed Atroposelective C−H Alkynylation. *Angew. Chem., Int. Ed.* **2018**, *57*, 3661−3665. (l) Xu, J.; Liu, Y.; Zhang, J.; Xu, X.; Jin, Z. Palladium-catalyzed enantioselective C(sp^2)−H arylation of ferrocenyl ketones enabled by a chiral transient directing group. *Chem. Commun.* **2018**, *54*, 689−692. (m) Park, H.; Verma, P.; Hong, K.; Yu, J.-Q. Controlling Pd(iv) reductive elimination pathways enables Pd(ii)-catalysed enantioselective C(sp^3)−H fluorination. *Nat. Chem.* **2018**, *10*, 755−762. (n) Wang, J.; Dong, C.; Wu, L.; Xu, M.; Lin, J.; Wei, K. Palladium-Catalyzed β-C−H Arylation of Ketones Using Amino Amide as a Transient Directing Group: Applications to Synthesis of Phenanthridinone Alkaloids. *Adv. Synth. Catal.* **2018**, *360*, 3709−3715. (o) Li, B.; Seth, K.; Niu, B.; Pan, L.; Yang, H.; Ge, H. Transient-Ligand-Enabled ortho-Arylation of Five-Membered Heterocycles: Facile Access to Mechanochromic Materials. *Angew. Chem., Int. Ed.* **2018**, *57*, 3401−3405. (p) Tang, M.; Yu, Q.; Wang, Z.; Zhang, C.; Sun, B.; Yi, Y.; Zhang, F.-L. Synthesis of Polycyclic Aromatic Hydrocarbons (PAHs) via a Transient Directing Group. *Org. Lett.* **2018**, *20*, 7620−7623. (q) Chen, X.-Y.; Sorensen, E. J. Pd-Catalyzed, ortho C−H Methylation and Fluorination of Benzaldehydes Using Orthanilic Acids as Transient Directing Groups. *J. Am. Chem. Soc.* **2018**, *140*, 2789−2792. (r) Liao, G.; Li, B.; Chen, H.-M.; Yao, Q.-J.; Xia, Y.-N.; Luo, J.; Shi, B.-F. Pd-Catalyzed Atroposelective C−H Allylation through β-O Elimination: Diverse Synthesis of Axially Chiral Biaryls. *Angew. Chem., Int. Ed.* **2018**, *57*, 17151−17155. (s) Dong, C.; Wu, L.; Yao, J.; Wei, K. Palladium-Catalyzed β-C−H Arylation of Aliphatic Aldehydes and Ketones Using Amino Amide as a Transient Directing Group. *Org. Lett.* **2019**, *21*, 2085−2089. (t) Liao, G.; Chen, H.-M.; Xia, Y.-N.; Li, B.; Yao, Q.-J.; Shi, B.-F. Synthesis of Chiral Aldehyde Catalysts by Pd-Catalyzed Atroposelective C−H Naphthylation. *Angew. Chem., Int. Ed.* **2019**, *58*, 11464−11468. (u) St John-Campbell, S.; Bull, J. A. Intramolecular palladium(ii)/(iv) catalysed C(sp^3)−H arylation of tertiary aldehydes using a transient imine directing group. *Chem. Commun.* **2019**, *55*, 9172−9175.

(5) (a) Liu, Y.; Ge, H. Site-selective C−H arylation of primary aliphatic amines enabled by a catalytic transient directing group. *Nat. Chem.* **2017**, *9*, 26−32. (b) Wu, Y.; Chen, Y.-Q.; Liu, T.; Eastgate, M. D.; Yu, J.-Q. Pd-Catalyzed γ-C(sp^3)−H Arylation of Free Amines Using a Transient Directing Group. *J. Am. Chem. Soc.* **2016**, *138*, 14554−14557. (c) Xu, Y.; Young, M. C.; Wang, C.-P.; Magness, D. M.; Dong, G. Catalytic C(sp^3)−H Arylation of Free Primary Amines

DOI: 10.1021/acs.orglett.9b02650
Org. Lett. XXXX, XXX, XXX−XXX

with an exo Directing Group Generated In Situ. *Angew. Chem., Int. Ed.* **2016**, *55*, 9084−9087. (d) Yada, A.; Liao, W.; Sato, Y.; Murakami, M. Buttressing Salicylaldehydes: A Multipurpose Directing Group for C(sp^3)−H Bond Activation. *Angew. Chem., Int. Ed.* **2017**, *56*, 1073−1076. (e) Lin, H.; Wang, C.; Bannister, T. D.; Kamenecka, T. M. Site-Selective γ-C(sp^3)−H and γ-C(sp^2)−H Arylation of Free Amino Esters Promoted by a Catalytic Transient Directing Group. *Chem. - Eur. J.* **2018**, *24*, 9535−9541. (f) Chen, Y.-Q.; Wang, Z.; Wu, Y.; Wisniewski, S. R.; Qiao, J. X.; Ewing, W. R.; Eastgate, M. D.; Yu, J.-Q. Overcoming the Limitations of γ- and δ-C−H Arylation of Amines through Ligand Development. *J. Am. Chem. Soc.* **2018**, *140*, 17884−17894.

(6) Jones, W. D. On the Nature of Carbon−Hydrogen Bond Activation at Rhodium and Related Reactions. *Inorg. Chem.* **2005**, *44*, 4475−4484.

(7) For selected examples, see: (a) Chen, X.; Goodhue, C. E.; Yu, J.-Q. Palladium-Catalyzed Alkylation of sp^2 and sp^3 C−H Bonds with Methylboroxine and Alkylboronic Acids: Two Distinct C−H Activation Pathways. *J. Am. Chem. Soc.* **2006**, *128*, 12634−12635. (b) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. Palladium-Catalyzed Methylation and Arylation of sp^2 and sp^3 C−H Bonds in Simple Carboxylic Acids. *J. Am. Chem. Soc.* **2007**, *129*, 3510−3511. (c) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. Site-Selective sp^2 and Benzylic sp^3 Palladium-Catalyzed Direct Arylation. *J. Am. Chem. Soc.* **2008**, *130*, 3266−3267. (d) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. Pd^{II}-Catalyzed Enantioselective Activation of C(sp^2)−H and C(sp^3)−H Bonds Using Monoprotected Amino Acids as Chiral Ligands. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882−4886. (e) Shabashov, D.; Daugulis, O. Auxiliary-Assisted Palladium-Catalyzed Arylation and Alkylation of sp^2 and sp^3 Carbon−Hydrogen Bonds. *J. Am. Chem. Soc.* **2010**, *132*, 3965−3972. (f) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. Highly Efficient Syntheses of Azetidines, Pyrrolidines, and Indolines via Palladium Catalyzed Intramolecular Amination of C(sp^3)−H and C(sp^2)−H Bonds at γ and δ Positions. *J. Am. Chem. Soc.* **2012**, *134*, 3−6. (g) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. Efficient Alkyl Ether Synthesis via Palladium-Catalyzed, Picolinamide-Directed Alkoxylation of Unactivated C(sp^3)−H and C(sp^2)−H Bonds at Remote Positions. *J. Am. Chem. Soc.* **2012**, *134*, 7313−7316. (h) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. Scope and Limitations of Auxiliary-Assisted, Palladium-Catalyzed Arylation and Alkylation of sp^2 and sp^3 C−H Bonds. *J. Org. Chem.* **2013**, *78*, 9689−9714. (i) Zhu, R.-Y.; He, J.; Wang, X.-C.; Yu, J.-Q. Ligand-Promoted Alkylation of C(sp^3)−H and C(sp^2)−H Bonds. *J. Am. Chem. Soc.* **2014**, *136*, 13194−13197. (j) Sattar, M.; Kumar, S. Palladium-Catalyzed Removable 8-Aminoquinoline Assisted Chemo- and Regioselective Oxidative sp^2-C−H/sp^3-C−H Cross-Coupling of Ferrocene with Toluene Derivatives. *Org. Lett.* **2017**, *19*, 5960−5963. (k) Tanji, Y.; Mitsutake, N.; Fujihara, T.; Tsuji, Y. Steric Effect of Carboxylate Ligands on Pd-Catalyzed Intramolecular C(sp^2)−H and C(sp^3)−H Arylation Reactions. *Angew. Chem., Int. Ed.* **2018**, *57*, 10314−10317.

(8) (a) Wu, X.; Zhao, Y.; Zhang, G.; Ge, H. Copper-Catalyzed Site-Selective Intramolecular Amidation of Unactivated C(sp^3)−H Bonds. *Angew. Chem., Int. Ed.* **2014**, *53*, 3706−3710. (b) Zang, Z.-L.; Zhao, S.; Karnakanti, S.; Liu, C.-L.; Shao, P.-L.; He, Y. Catalytic Multisite-Selective Acetoxylation Reactions at sp^2 vs sp^3 C−H Bonds in Cyclic Olefins. *Org. Lett.* **2016**, *18*, 5014−5017. (c) Zhu, R.-Y.; Liu, L.-Y.; Yu, J.-Q. Highly Versatile β-C(sp3)−H Iodination of Ke-tones Using a Practical Auxiliary. *J. Am. Chem. Soc.* **2017**, *139*, 12394−12397. (d) Ding, Q.; Ye, S.; Cheng, G.; Wang, P.; Farmer, M. E.; Yu, J.-Q. Ligand-Enabled meta-Selective C−H Arylation of Nosyl-Protected Phenethylamines, Benzylamines, and 2-Aryl Anilines. *J. Am. Chem. Soc.* **2017**, *139*, 417−425. (e) Mao, Y.-J.; Lou, S.-J.; Hao, H.-Y.; Xu, D. Selective C(sp^3)−H and C(sp^2)−H Fluorination of Alcohols Using Practical Auxiliaries. *Angew. Chem., Int. Ed.* **2018**, *57*, 14085−14089. (f) Xia, G.; Weng, J.; Liu, L.; Verma, P.; Li, Z.; Yu, J.-Q. Reversing conventional site-selectivity in C(sp^3)−H bond activation. *Nat. Chem.* **2019**, *11*, 571−577.

(9) Gou, B.-B.; Yang, H.; Sun, H.-R.; Chen, J.; Wu, J.; Zhou, L. Phenanthrene Synthesis by Palladium(II)-Catalyzed γ-C(sp^2)−H Arylation, Cyclization, and Migration Tandem Reaction. *Org. Lett.* **2019**, *21*, 80−84.

(10) (a) *Molecules and Medicine*; Corey, E. J., Czakò, B., Kürti, L., Eds.; John Wiley & Sons: Hoboken, NJ, 2007. (b) *Classics in Stereoselective Synthesis*; Carreira, E. M., Kvaerno, L., Eds.; Wiley-VCH: Weinheim, 2009.

(11) Yang, Y.-F.; Chen, G.; Hong, X.; Yu, J.-Q.; Houk, K. N. The Origins of Dramatic Differences in Five-Membered vs Six-Membered Chelation of Pd(II) on Efficiency of C(sp^3)−H Bond Activation. *J. Am. Chem. Soc.* **2017**, *139*, 8514−8521.

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