

Palladium-catalyzed oxidation of #-C(sp³)-H bond of primary alkylamines through a rare four-membered palladacycle intermediate

Bo Su, Ala Bunescu, Yehao Qiu, Stephan J. Zuend, Martin Ernst, and John F. Hartwig

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.0c01629 • Publication Date (Web): 27 Mar 2020

Downloaded from pubs.acs.org on March 27, 2020

Just Accepted

“Just Accepted” manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides “Just Accepted” as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. “Just Accepted” manuscripts appear in full in PDF format accompanied by an HTML abstract. “Just Accepted” manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). “Just Accepted” is an optional service offered to authors. Therefore, the “Just Accepted” Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these “Just Accepted” manuscripts.

Palladium-catalyzed oxidation of β -C(sp³)-H bond of primary alkylamines through a rare four-membered palladacycle intermediate

Bo Su^a, Ala Bunescu^{a,‡}, Yehao Qiu^{a,‡}, Stephan J. Zuend^b, Martin Ernst^c, and John F. Hartwig^{a,*}

^aDepartment of Chemistry, University of California, Berkeley, Berkeley, California 94720, United States

^bBASF Corp., 46820 Fremont Boulevard, Fremont, California 94538, United States

^cBASF SE, Carl-Bosch-Straße 38, 67056 Ludwigshafen, Germany

[‡]Contributed equally

ABSTRACT: Site-selective functionalizations of C-H bonds are often achieved with a directing group that leads to five- or six-membered metallacyclic intermediates. Analogous reactions that occur through four-membered metallacycles are rare. We report a challenging palladium-catalyzed oxidation of primary C-H bonds β to nitrogen in an imine of an aliphatic amine, a process that occurs through a four-membered palladacyclic intermediate. The success of the reaction relies on the identification, by a study on H/D exchange, of a simple directing group (salicylaldehyde) capable of inducing the formation of this small ring. To gain insight into the mechanism of this unusual oxidation reaction, a series of mechanistic experiments and DFT calculations were conducted. The experimental studies showed that cleavage of the C-H bond is rate-limiting, and formation of the strained four-membered palladacycle is thermodynamically uphill. DFT calculations corroborated these conclusions and suggested that the presence of an intramolecular hydrogen bond between the oxygen of the directing group and hydroxyl group of the ligating acetic acid that is crucial for stabilization of the palladacyclic intermediate.

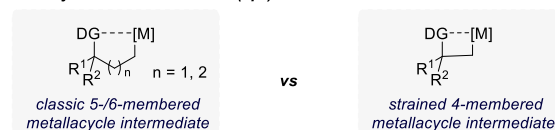
Introduction

Aliphatic amines are important organic compounds that are widely found in natural products, pharmaceuticals, and agrochemicals.¹ Therefore, the development of synthetic methods that enable efficient synthesis or functionalization of aliphatic amines has been a longstanding goal.² The functionalization of C(sp³)-H bond in alkylamines³ and their derivatives^{4,3h,5} by transition-metal complexes has been pursued because it can transform ubiquitous inert C(sp³)-H bonds of these molecules to valuable functional groups that are usually inaccessible or difficult to introduce by traditional methods.

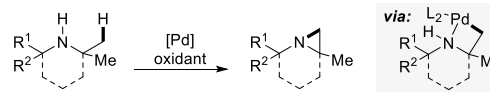
Cyclometallation is a crucial step in the functionalization of C-H bonds at specific sites by transition-metal catalysts.⁶ A wide range of directing groups have been developed to promote cyclometallation to form stable five- or six-membered metallacyclic intermediates (Figure 1a, top left). Such cyclometallation with alkylamines and their derivatives have led to the functionalization at C-H bonds γ - or δ - to the nitrogen atom.^{6c} In contrast, reactions that occur by C-H bond activation to form four-membered metallacycles are rare because formation of a strained-ring intermediate is kinetically and thermodynamically less favorable (Figure 1a, top right). Thus, functionalization of an alkylamine derivative at the C-H bond β to nitrogen is challenging,^{3a,3c,g,7,5l,8} and corresponding four-membered metallacycles are only known in specific cases.^{3a,3c} For example, Gaunt and coworkers reported a seminal palladium-catalyzed, β -C(sp³)-H activation of alkylamines directed by the amine nitrogen to form strained aziridine derivatives; however, the amines were limited to sterically hindered, secondary amines (Figure 1a, bottom).^{3a}

Scheme 1. Transition metal-catalyzed C-H functionalization of aliphatic amines

a) metallacycles involved in the C(sp³)-H bond functionalization



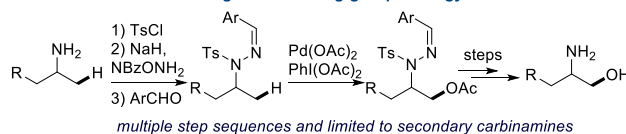
— Gaunt: rare example of 4-membered palladacycle intermediate —



limited to specific, sterically hindered secondary amines

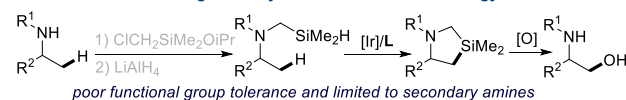
b) synthesis of 1,2-amino alcohols via metal-catalyzed -C(sp³)-H activation

— Dong: exo-directing-group strategy —



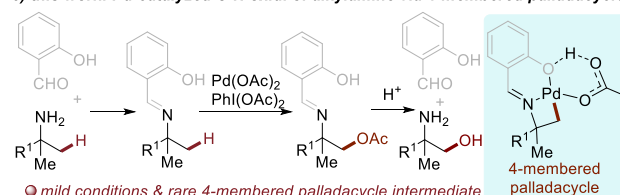
multiple step sequences and limited to secondary carbinamines

— Hartwig: C-H silylation and oxidation strategy —



poor functional group tolerance and limited to secondary amines

c) this work: Pd-catalyzed C-H oxid. of alkylamine via 4-membered palladacycle



● mild conditions & rare 4-membered palladacycle intermediate

● simple, readily installable, removable and recoverable directing group

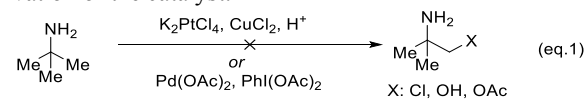
To achieve the functionalization of β -C(sp³)-H bonds in alkylamine derivatives, other more circuitous pathways have been developed, but none of these involve four-membered metallacyclic intermediates.^{51,8-9} For example, Dong and coworkers reported a palladium-catalyzed acetoxylation of β -C(sp³)-H bond of alkylamines to form 1,2-amino alcohol derivatives by converting the alkylamines to hydrazone derivatives, but this method is limited to secondary carbinamines, requires three steps to install the directing group on the nitrogen of the amine, and requires two steps to remove the directing group after the C-H acetoxylation (Figure 1b).⁵¹ Our group recently developed an iridium-catalyzed intramolecular silylation of the β -C(sp³)-H bonds of secondary amines.⁸ In combination with oxidation of the C-Si bond, this reaction creates an alternative approach to form 1,2-amino alcohols, but preparation of the hydrosilane was required and the functional group tolerance of the synthesis of this silane with LiAlH₄ would limit application of this process. Thus, functionalizations that occur through four-membered metallacycles and direct oxidations of the β -C(sp³)-H bonds of alkylamine derivatives are needed.

Here, we report an imine-directed acetoxylation of the β -C(sp³)-H bonds of tertiary carbinamines under mild, neutral reaction conditions by the formation of a four-membered palladacyclic intermediate (Scheme 1c). The appropriate imine (from salicylaldehyde)^{5b,5g} was revealed by initial studies on H/D exchange, and this directing group is inexpensive, readily installed, removed and recovered. Mechanistic studies show C-H bond cleavage is rate-limiting, and formation of the strained four-membered palladacycle is thermodynamically uphill.

Results and Discussion

1. Preliminary studies on the undirected C-H oxidation of *tert*-butyl amine.

tert-Butyl amine, the simplest tertiary carbinamine, was selected as the model substrate to investigate the β -C(sp³)-H oxidation of primary alkylamines because of the utility of the corresponding oxidation product, 2-amino-2-methylpropanol (AMP).¹⁰ Preliminary investigations focused on reported conditions for platinum- and palladium-catalyzed C(sp³)-H oxidation of free amines,^{11, 12} but no product derived from C-H bond functionalization was observed (eq. 1). The lack of reactivity of *tert*-butyl amine in the presence of the platinum catalyst in acid could be explained by the combination of steric hindrance and electron-poor property of the C-H bond of the protonated amine.¹¹ The lack of reactivity in the presence of the palladium catalyst under more neutral conditions can be attributed to coordination of *tert*-butyl amine, leading to deactivation of the catalyst.⁷

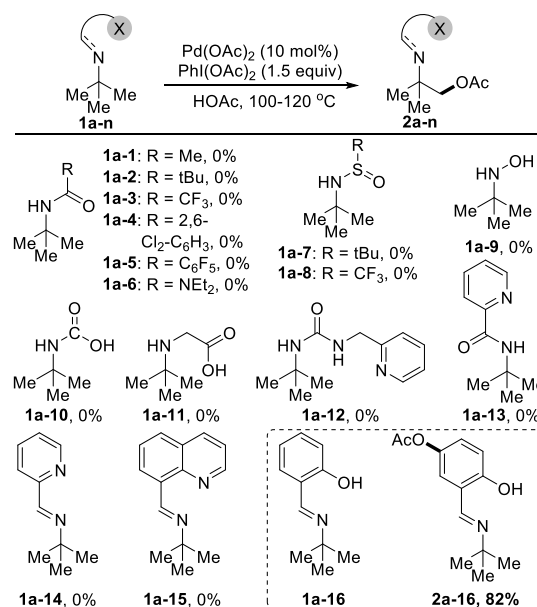


2. Identification of a suitable directing group.

Further studies involving directing groups^{6c} on nitrogen led to functionalization of the β -C-H bond, but the reactions required substantial investigation. A series of auxiliary groups were installed on the nitrogen of *tert*-butyl amine to form the corresponding amine derivatives **1a-1** to **1a-16** (Table 1). Under commonly employed conditions for the acetoxylation of C(sp³)-H bonds (10 mol% Pd(OAc)₂, 1.2 equiv of PhI(OAc)₂, in AcOH at 100-120 °C),^{4b,4c,13} none of the reactions of **1a-1** to **1a-15** gave any detectable product from acetoxylation; the reaction with **1a-16** gave the product from acetoxylation at the C(sp²)-H bond para

to the hydroxyl group of the imine to form **2a-16** in 82% yield without evidence for reaction at the C(sp³)-H bond.

Table 1. Pd-catalyzed C-H acetoxylation of amine derivatives



We considered two possible origins of the lack of reactivity of amine derivatives **1a-1** to **1a-15** and lack of reactivity of **1a-16** at the alkyl C-H bond based on the typical mechanism for palladium-catalyzed directed C-H oxidation (Figure 1). First, cleavage of the C(sp³)-H bond might not occur because the barrier to formation of a four-membered palladacycle **B** is too high. Second, C(sp³)-H cleavage could occur, but the transition state energy for subsequent oxidation of the Pd(II) intermediate **B** to the Pd(IV) intermediate **C** is too high or formation of the palladacycle **C** is too endothermic.

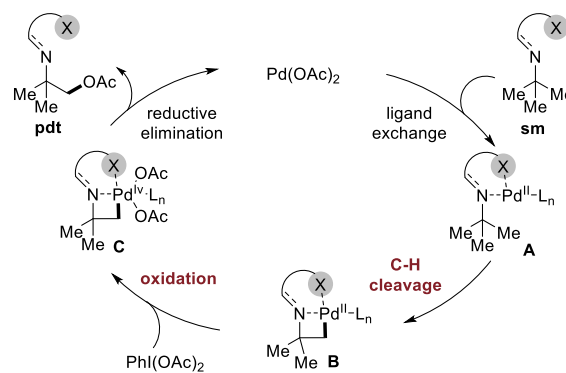


Figure 1. Proposed catalytic cycle for the β -C-H functionalization

To distinguish between these possibilities, a set of H/D-exchange experiments was conducted in the absence of oxidant (Scheme 2). The combination of *tert*-butyl amine derivatives **1a-1** to **1a-16**, Pd(OAc)₂ (10 mol%), and AcOD (2.0 equiv) were heated in CHCl₃ at 80 °C for 12 h. No detectable incorporation of deuterium into **1a-1** to **1a-15** was observed by ²H NMR spectroscopy, showing that cleavage of the C-H bond in these substrates does not occur. In contrast, H/D exchange with **1a-16** occurred at the C(sp³)-H bonds; 9.3% of the hydrogen atoms in the *tert*-butyl group of **1a-16** were deuteriated, indicating that the C(sp³)-H bond activation

occurred with the imine derived from salicylaldehyde. These data indicate that cleavage of the C(sp³)-H bond in **1a-16** occurs under more neutral conditions without activation of the aryl C-H bond that underwent oxidation in neat acetic acid. Yu recently investigated salicylaldehyde and its analogs systematically as a transient directing group for the arylation of the γ -C-H bonds in alkylamines.^{5g,5k} However, the functionalization of the β -C-H bond in alkylamines with these type of directing groups or others (eg. picolinic acid, 8-quinolinecarbaldehyde, etc.) has not been observed.

Scheme 2. H/D exchange experiments

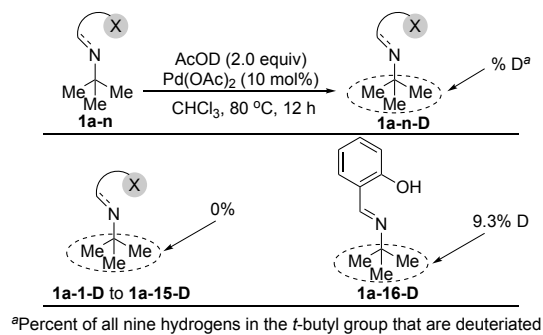


Table 2. Evaluation of the conditions for the acetoxylation of compound 1a

entry	additive	solvent	2a%	mono:di
1	NaOAc (1.5 equiv)	CHCl ₃	48%	2.2:1
2	NaOAc (1.5 equiv)	<i>m</i> -xylene	34%	8:1
3	NaOAc (1.5 equiv)	benzene	51%	4:1
4	NaOAc (1.5 equiv)	toluene	34%	10:1
5	NaOAc (1.5 equiv)	THF	7%	>20:1
6	NaOAc (1.5 equiv)	dioxane	14%	>20:1
7	NaOAc (1.5 equiv)	EA	28%	8:1
8	NaOAc (1.5 equiv)	MeCN	25%	7:1
9	NaOAc (1.5 equiv)	DMF	4%	>20:1
10	NaOAc (1.5 equiv)	DMPU	0%	----
11	Na ₂ HPO ₄ (1.5 equiv)	benzene	48%	3.8:1
12	KH ₂ PO ₄ (1.5 equiv)	benzene	49%	4:1
13	PhSO ₃ Na (1.5 equiv)	benzene	51%	4:1
14	----	benzene	48%	4:1
15	N-Boc-Ala (10 mol%)	benzene	58%	4:1

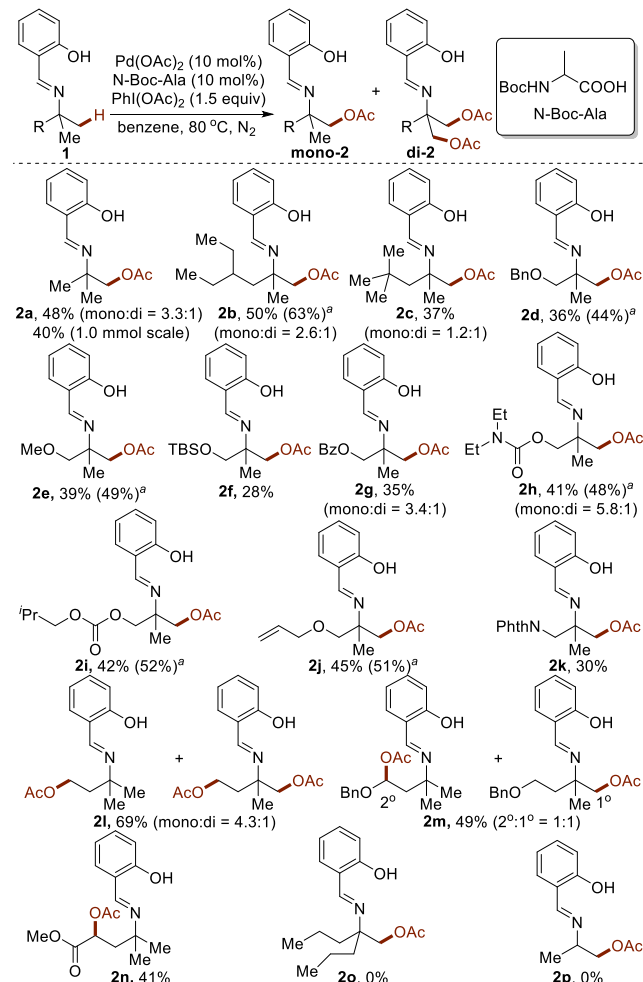
Conditions: reaction was conducted with **1a** (0.1 mmol), Pd(OAc)₂ (10 mmol%), and PhI(OAc)₂ (1.5 equiv) in solvent (1.0 mL) at 80 °C under N₂; the yields and ratio of **mono-2a** vs **di-2a** were determined by gas chromatography (GC) with dodacane as the internal standard; Abbreviations: ethyl acetate (EA), dimethylformamide (DMF), N, N'-dimethylpropyleneurea (DMPU).

3. Development of the β -C(sp³)-H bond acetoxylation.

Having shown that the C(sp³)-H bond of the salicylaldehyde imine **1a-16** (hereafter abbreviated as **1a**) undergoes cleavage, we considered that solvent and acidity could influence the selectivity for functionalization of the sp² versus sp³ C-H bonds (compare results in Table 1 and Scheme 2) and enable oxidation of the Pd-C bond of palladacycle **B**. Indeed, in the absence of acetic acid in nonpolar solvents, the product from acetoxylation of the C(sp³)-H bond was obtained (Table 2). Among the reactions conducted in non-polar solvents, the reaction in

benzene gave a 4:1 mixture of acetoxylation products **mono-2a** and **di-2a** in a combined 51% yield (entry 3). Reactions conducted with a series of added bases showed that weak bases had little effect on the yield (entries 3, 11-14). Reactions with some of the ligands¹⁴ currently used for palladium-catalyzed oxidation showed that the reaction with *N*-(*tert*-butoxycarbonyl)-L-alanine (*N*-Boc-Ala) occurred in a slightly higher 58% yield than that without ligand (51%) (entry 15, see supporting information for more details). In this reaction 10-20% of the reactant remained, leading to a mass balance of 70-80%; no side product formed in greater than 5% yield.

Table 3. Scope of the β -acetoxylation of amine derivatives



4. Scope of the β -C(sp³)-H bond acetoxylation.

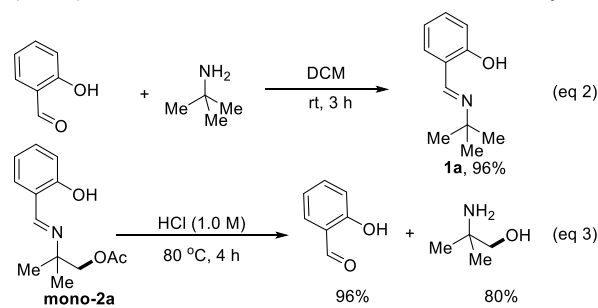
The scope of the acetoxylation of amines under the developed conditions via imine **1a** is shown in Table 3. Reactions of imines from tertiary carbinamines containing a range of substitution patterns and functional groups on the amine afforded isolated products from acetoxylation of the β -C(sp³)-H bonds in moderate yields. In most cases, conversion of the starting substrate was greater than 80%; the mass balance consisted of multiple products from side reactions. The acetoxylation of the β -C(sp³)-H bond of imines **1a-1c** bearing a series of alkyl substituents afforded the corresponding products (**2a-2c**). The ratio of mono-acetoxylation product to di-acetoxylation product was higher for the examples containing a smaller alkyl substituent. The acetoxylation also occurred in the presence of a variety of

functional groups (**1d-1k**), including benzyl and alkyl ethers (**1d** and **1e**), a silyl ether (**1f**), an ester (**1g**), a carbamate (**1h**), a carbonate (**1i**), an alkene (**1j**), and an amide (**1k**). The yield from acetoxylation on a larger scale was similar to that on smaller scale (Table 3, substrate **1a**).

The regioselectivity and yield for the acetoxylation depended on the architecture of the alkyl group. Acetoxylation of **1l**, which contains both γ - and β -methyl C-H bonds, occurred predominantly at the γ -methyl C-H bonds through a more favorable five-membered palladacycle intermediate. The site of acetoxylation of **1m** and **1n**, which contain both secondary γ -C(sp³)-H bonds and unactivated primary β -C(sp³)-H bonds, depended on the nature of the substituents on the secondary carbon. Reaction of **1m** containing a benzyloxy substituent at the γ methylene position gave a 1:1 mixture of products from reaction at the primary β -C(sp³)-H bond and secondary γ -C(sp³)-H bond, while reaction with substrate **1n** containing an alkoxycarbonyl group at the γ methylene position gave the product from acetoxylation at the acidic secondary γ -C(sp³)-H bond exclusively.¹⁵ Imine **1o** containing a single β methyl group and imine **1p** derived from a secondary, rather than tertiary, carbinamine did not react.

5. Installation, removal and recovery of the directing group.

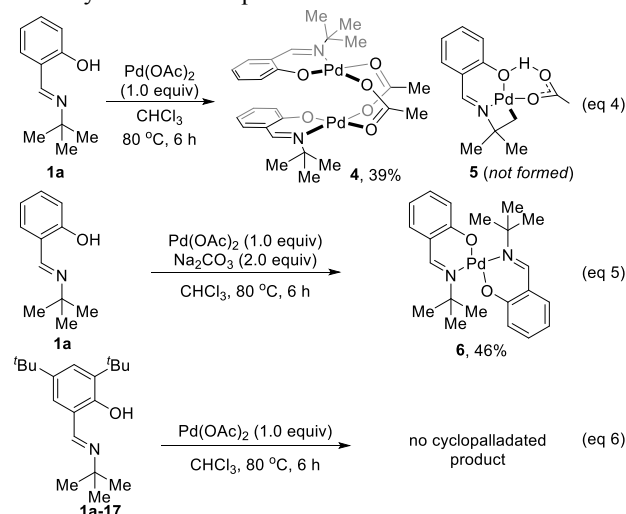
Installation and removal of the directing group are efficient and operationally simple, and the directing group is recoverable. The imine **1a** was obtained almost quantitatively (96%) by condensation of *tert*-butyl amine with salicylaldehyde in DCM at room temperature (eq 2). To demonstrate the ability to remove and recover the directing group, **mono-2a** was subjected to a 1.0 M aqueous solution of HCl at 80 °C (eq 3). The salicylaldehyde was removed and recovered in 96% yield, based on the amount of **mono-2a**. After basification of the aqueous solution, followed by extraction by organic solvent (DCM), the free amino alcohol was obtained in 80% yield.



6. Mechanistic investigation.

To determine whether cleavage of the C-H bond or oxidation of the Pd-C bond is rate-limiting and to gain insight into the thermodynamics for formation of the four-membered palladacycle, we conducted synthetic organometallic studies of cyclopalladated species. Reaction of imine **1a** with 1.0 equiv of Pd(OAc)₂ at 80 °C formed a dinuclear bis- μ -acetatopalladium complex **4** in 39% yield. No cyclopalladated complex **5** formed (eq 4). The same reaction in the presence of base (e.g. Na₂CO₃) to promote the C-H bond cleavage formed the palladium complex **6** containing two deprotonated salicyldimines, but, again, no cyclopalladated species formed (eq 5). Stoichiometric reactions were also conducted with **1a-17** that contains a bulky *tert*-butyl substituent at the ortho position of the hydroxyl group on the aryl group, but the cyclopalladated species was again absent (entry 6). To potentially stabilize the four-membered palladium intermediate,

external ligands, such as triphenyl phosphine and pyridine, were added to the reaction of **1a** with Pd(OAc)₂, but no palladacycle formed from cleavage of the C(sp³)-H bond. Consistent with these synthetic studies, no palladacyclic intermediate was observed during the catalytic reactions (eq 4-6), as judged by analysis of the crude reaction mixture by ¹H NMR spectroscopy. This set of mechanistic studies suggest that the formation of the four-membered palladacycle is unfavorable and could lie uphill from the salicyldimine complex **4**.



To test if a salicyldimine-ligated palladium is capable of forming a metallacycle by cleavage of a C(sp³)-H bond, we allowed Pd(OAc)₂ to react with substrate **1l** that could form a five-membered palladacycle under the same conditions as the reaction with **1a**. Indeed, the five-membered palladium complex **5'** formed in quantitative yield, as determined by ¹H NMR spectroscopy (eq 7). Although complex **5'** is stable in solution, it decomposed during attempts to purify by various methods. Thus, an external ligand (3,5-bis(trifluoromethyl)phenyl)phosphine was added to the crude reaction mixture of **5'** to form a more stable complex **7**, which was isolated by silica gel column chromatography in 86% yield. The structures of palladium complexes **4**, **6**, and **7** were confirmed by X-ray crystallography (Figure 2).

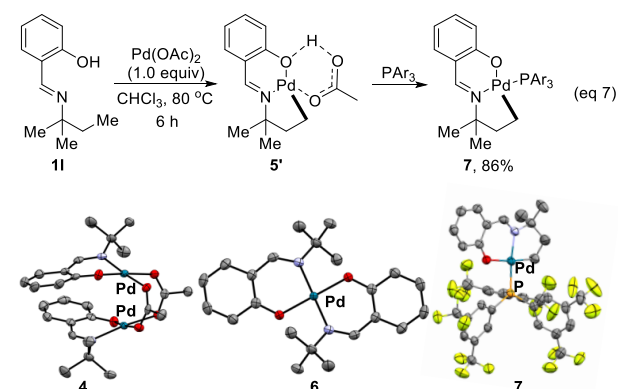
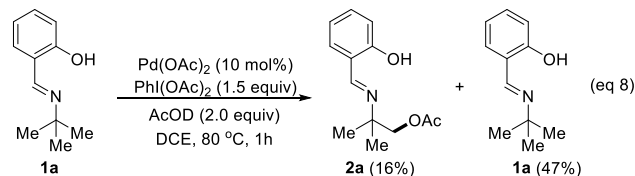


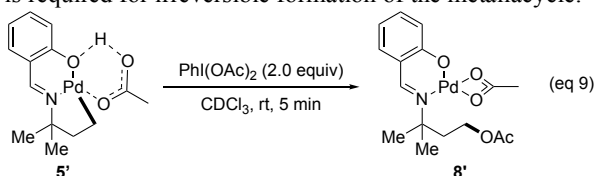
Figure 2. Solid-state structures of **4, **5**, and **7** determined by single crystal X-ray diffractions.**

To probe whether the β -C(sp³)-H bond was cleaved reversibly under the conditions of the acetoxylation, we ran the catalytic reaction of **1a** in the presence of 2.0 equiv of AcOD and 1.5 equiv of PhI(OAc)₂ to partial conversion. After 1 h at 80 °C (eq 8), ¹H NMR analysis of the crude reaction mixture showed

that 47% of the starting material **1a** remained (16% of the acetoxyated product **2a** formed), and no deuterium had been incorporated into the unreacted **1a**, as determined by ^2H NMR spectroscopy. These data indicate that the C-H cleavage is irreversible and, therefore, that oxidation of the metallacyclic intermediate is more rapid than reversion to the acyclic precursor.



To gauge the rate of the oxidation of a palladacycle derived from the salicylaldimines, we studied the oxidation of the five-membered metallacycle **5'** generated in solution (eq 9). The reaction of **5'** with 2 equiv of $\text{PhI}(\text{OAc})_2$ occurred to completion at room temperature in less than 5 min to form the *C* acetoxyated complex in 46-50% yield. These data are consistent with rapid oxidation of the four-membered palladacycle at 80 °C that is required for irreversible formation of the metallacycle.



7. DFT calculations of the catalytic acetoxylation. To gain insight into the thermodynamics for formation of a four-membered metallacycle, we performed DFT calculations on the catalytic acetoxylation process. These data are summarized in Figure 3. We determined the barrier and thermodynamics for cleavage of the β C-H bond of the bound salicylalimine by a concerted metallation deprotonation process involving the coordinated acetate in the monomeric complexes **9** and **9'** derived from the isolated dimeric complexes **4** and **4'**. Quasi-harmonic Gibbs free energies were calculated of the observed dimeric salicylalimine palladium complexes **4** and **4'**, the monomeric **9** and **9'** that would undergo C-H bond cleavage, the transition states for C-H activation by **9** and **9'** (**TS(9-10)** and **TS(9'-10')**) to form palladacycles **10** and **10'** containing a bound acetic acid, and palladacycles **5** and **5'**, which are isomers of **10** and **10'**, in which the carboxylic acid is engaged in an intramolecular hydrogen bond. These calculations showed that formation of the four-membered metallacycle is endergonic, but formation of the five-membered metallacycle is exergonic.

The free energy barriers for C-H activation within complexes **9** and **9'** to form the four-membered and five-membered palladacycles **10** and **10'** are 22.5 and 17.9 kcal/mol, respectively. The computed thermodynamics for the formation of the metallacycle depended strongly on the presence or absence of an intramolecular hydrogen bond involving the coordinated acetic acid. The computed energy of the four-membered palladacycle **5** containing the hydrogen bond is lower in energy than palladacycle **10** lacking the hydrogen bond

by 13.8 kcal/mol. The computed difference in energy between the analogous structures **5'** and **10'** containing the hydrogen bond is 14.2 kcal/mol. Thus, the formation of the four-membered palladacycle **5** is computed to be thermodynamically uphill of monomeric salicylalimine complex **9** by 1.3 kcal/mol and uphill of the isolated dimeric analog **4** by 10.6 kcal/mol, whereas formation of the five-membered palladacycle **5'** is computed to be downhill of monomeric **9'** by -8.8 kcal/mol and nearly thermoneutral with the dimeric complex **4'**. These results corroborate our experimental observation of the formation of five-membered palladacycle **5'** from **4'** but our detection of the formation of the four-membered ring palladacycle **5** only indirectly by H/D exchange experiments in the absence of oxidant (see Scheme 2).

DFT calculations on the remainder of the reaction pathway are included in Figure 3. Oxidation of both palladacycles **5** and **5'** by $\text{PhI}(\text{OAc})_2$ was computed to be thermodynamically downhill by ~20 kcal/mol. The resulting Pd(IV) intermediates **11** and **11'** are computed to undergo nearly thermoneutral dissociation of HOAc to form complexes **12** and **12'**, which subsequently undergo reductive elimination to form acetoxyated products **8** and **8'** in which the functionalized salicylalimine remains bound to palladium.¹⁶ The free energy barriers for reductive elimination from intermediates **12** and **12'** were calculated to be 12.2 and 15.4 kcal/mol, respectively. A comparison of these barriers to the 22.5 and 17.9 kcal/mol barriers for C-H bond cleavage imply that C-H activation is irreversible and turnover-limiting for the catalytic acetoxylation process. This conclusion is consistent with the lack of incorporation of deuterium into the reactant under the conditions of the catalytic process.

Conclusion

In conclusion, we developed a palladium-catalyzed, directed β -C(sp^3)-H acetoxylation of tertiary carbinamines, which likely proceeds through a rare four-membered palladacycle intermediate. Identification of the appropriate group on the nitrogen of the amine to enable C-H activation resulted from studies on the H/D exchange. The directing group is inexpensive, readily installed, removed, and recovered. Mechanistic studies revealed that the C(sp^3)-H bond is cleaved irreversibly and is the rate-determining step of the reaction. DFT calculations were consistent with experimental results in which the four-membered palladacycle was not observed during the reaction but five-membered palladacycles formed readily. The DFT studies suggest that formation of the four-membered palladacycle is thermodynamically uphill, but the formation of the corresponding five-membered palladacycle is downhill. The combination of directing group on nitrogen to facilitate formation of a four-membered metallacycle and oxidant that reacts rapidly with the unstable metallacycle enables this functionalization of the C-H bond of an amine to occur, and these principles should facilitate the discovery of additional reactions through such strained intermediates.

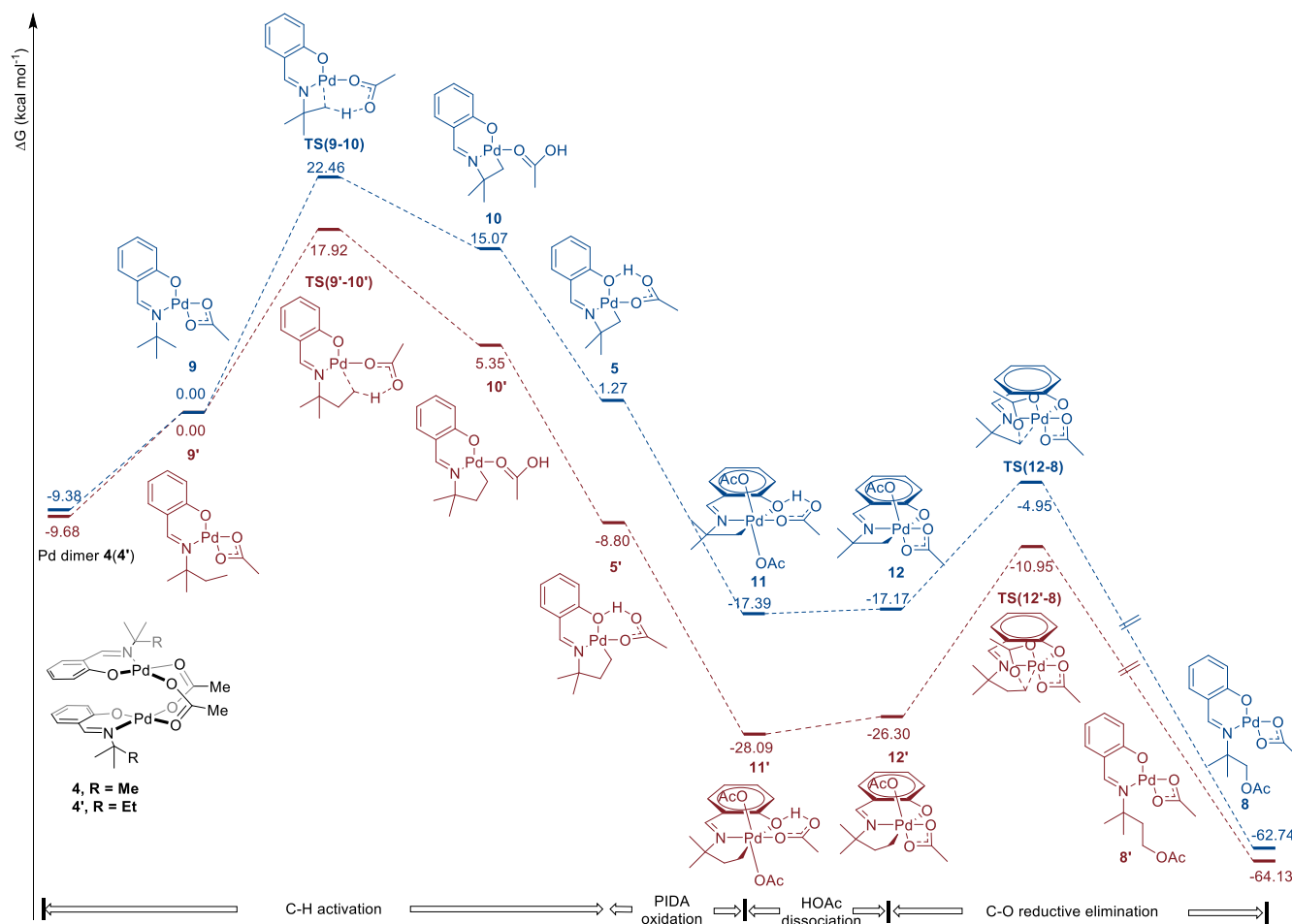


Figure 3. Quasi-harmonic Gibbs free energy ($T = 353.15$ K) profile of Pd-catalyzed α -acetoxylation of primary amines. Calculations were performed at the B3LYP-d3/LANL2DZ + 6-31G(d)/SMD(benzene)//M06-d3/SDD + 6-311+G(d,p)/SMD(benzene) level of theory.

ASSOCIATED CONTENT

Supporting Information.

“The supporting information is available free of charge via the Internet at <http://pubs.acs.org>.”

Experimental procedures, characterization of new compounds, X-ray data, and computational details (PDF)

X-ray crystallographic data for compounds **4** (CIF)

X-ray crystallographic data for compounds **6** (CIF)

X-ray crystallographic data for compounds **7** (CIF)

AUTHOR INFORMATION

Corresponding Author

* jhartwig@berkeley.edu

ORCID

Bo Su: 0000-0002-1184-0828

Ala Bunescu: 0000-0002-3880-8182

Yehao Qiu: 0000-0002-2650-0703

Stephan Zuend: 0000-0002-4420-000X

John F. Hartwig: 0000-0002-4157-468X.

ACKNOWLEDGMENT

This work was supported by BASF through the California Research Alliance (CARA) and Computation Facility at UC Berkeley for DFT calculations. We gratefully acknowledge Dr. Hasan Celik for

assistance with NMR experiments and Dr. Nicholas Settineri for X-ray crystallography. Instruments in the CoC-NMR are supported in part by NIH S10OD024998. AB thanks the Swiss National Science Foundation for a postdoctoral fellowship. BS thanks Dr. Yumeng Xi for helpful discussion.

REFERENCES

- (1) Prasat, K.; Chulabhorn, M.; Somsak, R. Alkaloids as Important Scaffolds in Therapeutic Drugs for the Treatments of Cancer, Tuberculosis, and Smoking Cessation *Curr. Top. Med. Chem.* **2014**, *14*, 239.
- (2) (a) Hager, A.; Vrielink, N.; Hager, D.; Lefranc, J.; Trauner, D. Synthetic approaches towards alkaloids bearing α -tertiary amines *Nat. Prod. Rep.* **2016**, *33*, 491; (b) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. Synthesis of secondary amines *Tetrahedron* **2001**, *57*, 7785.
- (3) (a) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. Palladium-catalysed C-H activation of aliphatic amines to give strained nitrogen heterocycles *Nature* **2014**, *510*, 129; (b) Calleja, J.; Pla, D.; Gorman, T. W.; Domingo, V.; Haffemayer, B.; Gaunt, M. J. A steric tethering approach enables palladium-catalysed C-H activation of primary amino alcohols *Nat Chem* **2015**, *7*, 1009; (c) He, C.; Gaunt, M. J. Ligand-Enabled Catalytic C-H Arylation of Aliphatic Amines by a Four-Membered-Ring Cyclopalladation Pathway *Angew. Chem. Int. Ed.* **2015**, *54*, 15840; (d) Willcox, D.; Chappell, B. G. N.; Hogg, K. F.; Calleja, J.; Smalley, A. P.; Gaunt, M. J. A general catalytic β -C-H carbonylation of aliphatic amines to β -lactams *Science* **2016**, *354*, 851; (e) Zakrzewski, J.; Smalley, A. P.; Kabeshov, M. A.; Gaunt, M. J.; Lapkin, A. A. Continuous-Flow Synthesis and Derivatization of

Aziridines through Palladium-Catalyzed C(sp³)-H Activation *Angew. Chem. Int. Ed.* **2016**, *55*, 8878; (f) Cabrera-Pardo, J. R.; Trowbridge, A.; Nappi, M.; Ozaki, K.; Gaunt, M. J. Selective Palladium(II)-Catalyzed Carbonylation of Methylene β-C-H Bonds in Aliphatic Amines *Angew. Chem. Int. Ed.* **2017**, *56*, 11958; (g) Smalley, A. P.; Cuthbertson, J. D.; Gaunt, M. J. Palladium-Catalyzed Enantioselective C-H Activation of Aliphatic Amines Using Chiral Anionic BINOL-Phosphoric Acid Ligands *J. Am. Chem. Soc.* **2017**, *139*, 1412; (h) He, C.; Whitehurst, W. G.; Gaunt, M. J. Palladium-Catalyzed C(sp³)-H Bond Functionalization of Aliphatic Amines *Chem* **2019**, *5*, 1031.

(4) (a) Wang, D.-H.; Hao, X.-S.; Wu, D.-F.; Yu, J.-Q. Palladium-Catalyzed Oxidation of Boc-Protected N-Methylamines with IOAc as the Oxidant: A Boc-Directed sp³ C-H Bond Activation *Org. Lett.* **2006**, *8*, 3387; (b) Neufeldt, S. R.; Sanford, M. S. O-Acetyl Oximes as Transformable Directing Groups for Pd-Catalyzed C-H Bond Functionalization *Org. Lett.* **2010**, *12*, 532; (c) Desai, L. V.; Hull, K. L.; Sanford, M. S. Palladium-Catalyzed Oxygenation of Unactivated sp³ C-H Bonds *J. Am. Chem. Soc.* **2004**, *126*, 9542; (d) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. Highly Regioselective Arylation of sp³ C-H Bonds Catalyzed by Palladium Acetate *J. Am. Chem. Soc.* **2005**, *127*, 13154; (e) He, G.; Chen, G. A Practical Strategy for the Structural Diversification of Aliphatic Scaffolds through the Palladium-Catalyzed Picolinamide-Directed Remote Functionalization of Unactivated C(sp³)-H Bonds *Angew. Chem. Int. Ed.* **2011**, *50*, 5192; (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(sp³)-H and C(sp²)-H Bonds at γ and δ Positions *J. Am. Chem. Soc.* **2012**, *134*, 3; (g) Nadres, E. T.; Daugulis, O. Heterocycle Synthesis via Direct C-H/N-H Coupling *J. Am. Chem. Soc.* **2012**, *134*, 7; (h) 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(sp³)-H and C(sp²)-H Bonds at Remote Positions *J. Am. Chem. Soc.* **2012**, *134*, 7313; (i) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. Palladium-Catalyzed Picolinamide-Directed Alkylation of Unactivated C(sp³)-H Bonds with Alkyl Iodides *J. Am. Chem. Soc.* **2013**, *135*, 2124; (j) Fan, M.; Ma, D. Palladium-Catalyzed Direct Functionalization of 2-Aminobutanoic Acid Derivatives: Application of a Convenient and Versatile Auxiliary *Angew. Chem. Int. Ed.* **2013**, *52*, 12152; (k) Ye, X.; He, Z.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. 1,2,3-Triazoles as versatile directing group for selective sp² and sp³ C-H activation: cyclization vs substitution *Chem. Sci.* **2013**, *4*, 3712; (l) Ling, P.-X.; Fang, S.-L.; Yin, X.-S.; Chen, K.; Sun, B.-Z.; Shi, B.-F. Palladium-Catalyzed Arylation of Unactivated γ-Methylene C(sp³)-H and δ-C-H Bonds with an Oxazoline-Carboxylate Auxiliary *Chem. Eur. J.* **2015**, *21*, 17503; (m) Zhang, L.-S.; Chen, G.; Wang, X.; Guo, Q.-Y.; Zhang, X.-S.; Pan, F.; Chen, K.; Shi, Z.-J. Direct Borylation of Primary C-H Bonds in Functionalized Molecules by Palladium Catalysis *Angew. Chem. Int. Ed.* **2014**, *53*, 3899; (n) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J.-Q. Ligand-enabled cross-coupling of C(sp³)-H bonds with arylboron reagents via Pd(II)/Pd(0) catalysis *Nat. Chem.* **2014**, *6*, 146.

(5) (a) Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. Palladium-catalyzed transannular C-H functionalization of alicyclic amines *Nature* **2016**, *531*, 220; (b) 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; (c) Zhan, B.-B.; Li, Y.; Xu, J.-W.; Nie, X.-L.; Fan, J.; Jin, L.; Shi, B.-F. Site-Selective δ-C(sp³)-H Alkylation of Amino Acids and Peptides with Maleimides via a Six-Membered Palladacycle *Angew. Chem. Int. Ed.* **2018**, *57*, 5858; (d) Shao, Q.; Wu, Q.-F.; He, J.; Yu, J.-Q. Enantioselective γ-C(sp³)-H Activation of Alkyl Amines via Pd(II)/Pd(0) Catalysis *J. Am. Chem. Soc.* **2018**, *140*, 5322; (e) Kapoor, M.; Liu, D.; Young, M. C. Carbon Dioxide-Mediated C(sp³)-H Arylation of Amine Substrates *J. Am. Chem. Soc.* **2018**, *140*, 6818; (f) Yang, Q.-L.; Li, Y.-Q.; Ma, C.; Fang, P.; Zhang, X.-J.; Mei, T.-S. Palladium-Catalyzed C(sp³)-H Oxygenation via Electrochemical Oxidation *J. Am. Chem. Soc.* **2017**, *139*, 3293; (g) Yada, A.; Liao, W.; Sato, Y.; Murakami, M. Buttressing Salicylaldehydes: A Multipurpose

Directing Group for C(sp³)-H Bond Activation *Angew. Chem. Int. Ed.* **2017**, *56*, 1073; (h) 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; (i) 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; (j) Xu, Y.; Young, M. C.; Wang, C.; Magness, D. M.; Dong, G. Catalytic C(sp³)-H Arylation of Free Primary Amines with an exo Directing Group Generated In Situ *Angew. Chem. Int. Ed.* **2016**, *55*, 9084; (k) Wu, Y.; Chen, Y.-Q.; Liu, T.; Eastgate, M. D.; Yu, J.-Q. Pd-Catalyzed γ-C(sp³)-H Arylation of Free Amines Using a Transient Directing Group *J. Am. Chem. Soc.* **2016**, *138*, 14554; (l) Huang, Z.; Wang, C.; Dong, G. A Hydrazone-Based exo-Directing-Group Strategy for β-C-H Oxidation of Aliphatic Amines *Angew. Chem. Int. Ed.* **2016**, *55*, 5299; (m) Li, B.; Li, X.; Han, B.; Chen, Z.; Zhang, X.; He, G.; Chen, G. Construction of Natural-Product-Like Cyclophane-Braced Peptide Macrocycles via sp³ C-H Arylation *J. Am. Chem. Soc.* **2019**, *141*, 9401; (n) Wang, H.; Tong, H.-R.; He, G.; Chen, G. An Enantioselective Bidentate Auxiliary Directed Palladium-Catalyzed Benzylic C-H Arylation of Amines Using a BINOL Phosphate Ligand *Angew. Chem. Int. Ed.* **2016**, *55*, 15387.

(6) (a) Kleiman, J. P.; Dubeck, M. The Preparation of Cyclopentadienyl [o-(Phenylazo)Phenyl]Nickel *J. Am. Chem. Soc.* **1963**, *85*, 1544; (b) Dehand, J.; Pfeffer, M. Cyclometallated compounds *Coord. Chem. Rev.* **1976**, *18*, 327; (c) Sambiagio, C.; Schönbauer, D.; Blicke, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A comprehensive overview of directing groups applied in metal-catalysed C-H functionalisation chemistry *Chem. Soc. Rev.* **2018**, *47*, 6603.

(7) Smalley, A. P.; Gaunt, M. J. Mechanistic Insights into the Palladium-Catalyzed Aziridination of Aliphatic Amines by C-H Activation *J. Am. Chem. Soc.* **2015**, *137*, 10632.

(8) Su, B.; Lee, T.; Hartwig, J. F. Iridium-Catalyzed, β-Selective C(sp³)-H Silylation of Aliphatic Amines To Form Silapyrrolidines and 1,2-Amino Alcohols *J. Am. Chem. Soc.* **2018**, *140*, 18032.

(9) (a) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. Expanding the substrate scope for C-H amination reactions: Oxidative cyclization of urea and guanidine derivatives *Org. Lett.* **2006**, *8*, 1073; (b) Olson, D. E.; Du Bois, J. Catalytic C-H amination for the preparation of substituted 1,2-diamines *J. Am. Chem. Soc.* **2008**, *130*, 11248; (c) Strambeanu, I.; White, M. C. Catalyst-Controlled C-O versus C-N Allylic Functionalization of Terminal Olefins *J. Am. Chem. Soc.* **2013**, *135*, 12032.

(10) Calleja, P.; Ernst, M.; Hashmi, A. S. K.; Schaub, T. Ruthenium-Catalyzed Deaminative Hydrogenation of Amino Nitriles: Direct Access to 1,2-Amino Alcohols *Chem. Eur. J.* **2019**, *25*, 9498.

(11) Lee, M.; Sanford, M. S. Platinum-Catalyzed, Terminal-Selective C(sp³)-H Oxidation of Aliphatic Amines *J. Am. Chem. Soc.* **2015**, *137*, 12796.

(12) Chen, K.; Wang, D.; Li, Z.-W.; Liu, Z.; Pan, F.; Zhang, Y.-F.; Shi, Z.-J. Palladium catalyzed C(sp³)-H acetoxylation of aliphatic primary amines to α-amino alcohol derivatives *Org. Chem. Front.* **2017**, *4*, 2097.

(13) (a) Zhang, J.; Khaskin, E.; Anderson, N. P.; Zavalij, P. Y.; Vedernikov, A. N. Catalytic aerobic oxidation of substituted 8-methylquinolines in Pd^{II}-2,6-pyridinedicarboxylic acid systems *Chem. Commun.* **2008**, 3625; (b) Ren, Z.; Mo, F.; Dong, G. Catalytic Functionalization of Unactivated sp³ C-H Bonds via exo-Directing Groups: Synthesis of Chemically Differentiated 1,2-Diols *J. Am. Chem. Soc.* **2012**, *134*, 16991; (c) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. Pd(II)-Catalyzed Primary-C(sp³)-H Acyloxylation at Room Temperature *Org. Lett.* **2012**, *14*, 3724; (d) Li, Q.; Zhang, S. Y.; He, G.; Nack, W. A.; Chen, G. Palladium-Catalyzed Picolinamide-Directed Acetoxylation of Unactivated γ-C(sp³)-H Bonds of Alkylamines *Adv. Synth. Catal.* **2014**, *356*, 1544.

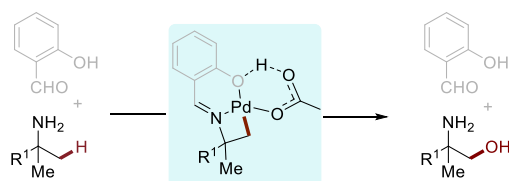
(14) (a) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Ligand-Accelerated C-H Activation Reactions: Evidence for a Switch of Mechanism *J. Am. Chem. Soc.* **2010**, *132*, 14137; (b) Engle, K. M.; Thuy-Boun, P. S.; Dang, M.; Yu, J.-Q. Ligand-Accelerated Cross-Coupling of C(sp²)-H Bonds with Arylboron Reagents *J. Am. Chem. Soc.* **2011**, *133*, 18183;

1 (c) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. Ligand-Enabled
2 Reactivity and Selectivity in a Synthetically Versatile Aryl C-H
3 Olefination *Science* **2010**, *327*, 315.

4 (15) (a) Aihara, Y.; Chatani, N. Nickel-Catalyzed Direct Alkylation
5 of C-H Bonds in Benzamides and Acrylamides with Functionalized
6 Alkyl Halides via Bidentate-Chelation Assistance *J. Am. Chem. Soc.*
7 **2013**, *135*, 5308; (b) Lu, H.; Hu, Y.; Jiang, H.; Wojtas, L.; Zhang, X.
8 P. Stereoselective Radical Amination of Electron-Deficient C(sp³)-H
9 Bonds by Co(II)-Based Metalloradical Catalysis: Direct Synthesis of
10 α -Amino Acid Derivatives via α -C-H Amination *Org. Lett.* **2012**, *14*,
11 5158.

(16) For other possible reductive elimination pathways, see: (a)
12 Buettner, C. S.; Willcox, D.; Chappell, B. G. N.; Gaunt, M. J.
13 Mechanistic investigation into the C(sp³)-H acetoxylation of
14 morpholinones *Chem. Sci.* **2019**, *10*, 83; (b) Nappi, M.; He, C.;
15 Whitehurst, W. G.; Chappell, B. G. N.; Gaunt, M. J. Selective
16 Reductive Elimination at Alkyl Palladium(IV) by Dissociative Ligand
17 Ionization: Catalytic C(sp³)-H Amination to Azetidines *Angew. Chem.*
18 *Int. Ed.* **2018**, *57*, 3178.

Table of Contents



- mild conditions & rare 4-membered palladacycle intermediate
 - simple, readily installable, removable and recoverable directing group
-