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Palladium-Catalyzed Oxidation of β-C(sp^3)–H Bonds of Primary Alkylamines through a Rare Four-Membered Palladacycle Intermediate

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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 palladacyclc intermediate. The success of the reaction relies on the identification, by H/D exchange, of a simple directing group (salicylaldehyde) capable of inducing

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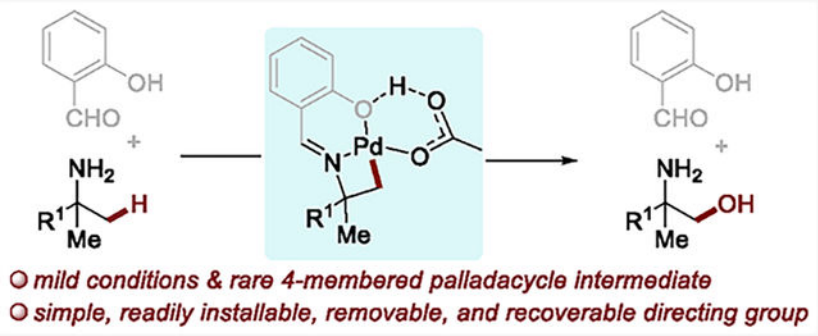
ASSOCIATED CONTENT
SI Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c01629.
Experimental procedures, characterization of new compounds, X-ray data, and computational details (PDF)
X-ray crystallographic data for compounds **4** (CIF)
X-ray crystallographic data for compounds **7** (CIF)
X-ray crystallographic data for compounds **6** (CIF)

the formation of this small ring. To gain insight into the steps of the catalytic cycle of this unusual oxidation reaction, a series of mechanistic experiments and density functional theory (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 is crucial for stabilization of the palladacyclic intermediate.

Graphical Abstract:



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 long-standing goal.[2] The functionalization of C(sp^3)–H bonds in alkylamines[3] and their derivatives[4,3h,5] by transition-metal complexes has been pursued because it can transform ubiquitous inert C(sp^3)–H bonds of these molecules to valuable functional groups that are usually inaccessible or difficult to introduce by traditional methods.

Cyclometalation 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 cyclometalation to form stable five- or six-membered metallacyclic intermediates (Scheme 1a, top left). Such cyclometalation with alkylamines and their derivatives has 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 (Scheme 1a, top right). Thus, functionalization of an alkylamine derivative at the C–H bond β to nitrogen is challenging,[3a,c–g,7,5l,8] and the corresponding four-membered metallacycles are only known in specific cases.[3a,c] For example, Gaunt and co-workers reported a seminal palladium-catalyzed, β-C(sp^3)–H activation of alkylamines directed by the amine nitrogen to form strained aziridine derivatives; however, the amines were limited to sterically hindered, secondary amines (Scheme 1a, bottom). [3a]

To achieve the functionalization of β-C(sp^3)–H bonds in alkylamine derivatives, other more circuitous pathways have been developed, but none of these involve four-membered

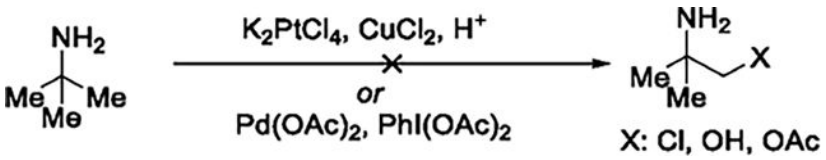
metallacyclic intermediates.[5l,8,9] For example, Dong and co-workers reported palladium-catalyzed acetoxylations of β-C(sp^3)–H bonds of alkylamines to form 1,2-amino alcohol derivatives by converting the alkylamines to hydrazone derivatives, but this method is limited to secondary carbinamines, requires 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 (Scheme 1b).[5l] Our group recently developed an iridium-catalyzed intramolecular silylation of the β-C(sp^3)–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 (Scheme 1b), but preparation of the hydrosilane was required and the functional group tolerance of the synthesis of this silane with $LiAlH_4$ would limit the application of this process. Thus, functionalizations that occur through four-membered metallacycles and direct oxidations of the β-C(sp^3)–H bonds of alkylamine derivatives are needed.

Here, we report an imine-directed acetoxylation of the β-C(sp^3)–H bonds of tertiary carbinamines under mild reaction conditions by the formation of a four-membered palladacyclic intermediate (Scheme 1c). The appropriate imine (from salicylaldehyde)[5b,g] 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 pallacacycle is thermodynamically uphill.

RESULTS AND DISCUSSION

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(sp^3)–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(sp^3)–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



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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]

Identification of a Suitable Directing Group.

Further studies involving directing groups[6c] on nitrogen led to functionalization of the β-C–H bond, but obtaining good yields of the oxidized product 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(sp^3)–H bonds (10 mol % $Pd(OAc)_2$, 1.2 equiv of $PhI(OAc)_2$, in AcOH at 100–120 °C),[4b,c,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(sp^2)–H bond para to the hydroxyl group of the imine to form **2a-16** in 82% yield without evidence for reaction at the C(sp^3)–H bond.

We considered two possible origins of the lack of reactivity of amine derivatives **1a-1** to **1a-15** and the 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(sp^3)–H bond might not occur because the barrier to formation of a four-membered palladacycle **B** is too high. Second, C(sp^3)–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.

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) was heated in $CHCl_3$ 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(sp^3)–H bonds; 9.3% of the hydrogen atoms in the *tert*-butyl group of **1a-16** were deuterated, indicating that the C(sp^3)–H bond activation occurred with the imine derived from salicaldehyde. These data indicate that cleavage of the C(sp^3)–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 analogues systematically as a transient directing group for the arylation of the γ-C–H bonds in alkylamines.[5g,k] However, the functionalization of the β-C–H bond in alkylamines with these types of directing groups or others (e.g., picolinic acid, 8-quinoline-carbaldehyde, etc.) has not been observed.

Development of the β-C(sp^3)–H Bond Acetoxylation.

Having shown that the C(sp^3)–H bond of the salicylaldimine **1a-16** (hereafter abbreviated as **1a**) undergoes cleavage, we considered that solvent and acidity could influence the selectivity for functionalization of the sp^2 versus sp^3 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(sp^3)–H bond was obtained (Table 2). Among the reactions conducted in nonpolar solvents, the reaction in benzene gave a 4:1 mixture of acetoxylated products **mono2a** and **di2a** 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 ligands[14] 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 the 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.

Scope of the β-C(sp^3)–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(sp^3)–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(sp^3)–H bond of imines **1a–1c** bearing a series of alkyl substituents afforded the corresponding products (**2a–2c**). The ratio of monoacetoxylation product to diacetoxylation 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**).

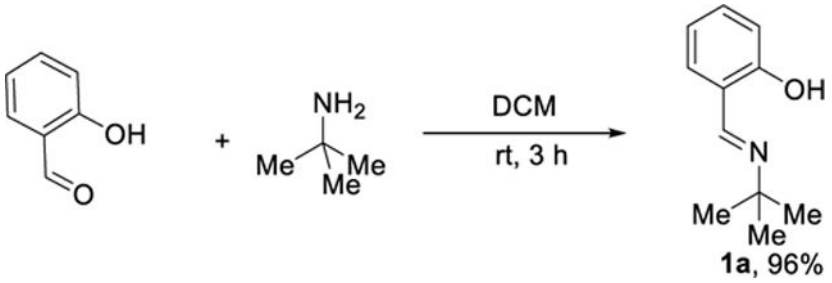
The regioselectivity and yield for the acetoxylation depended on the architecture of the alkyl group. Acetoxylation of **1l**, which contains both γ- and β-methyl C–H bonds, occurred predominantly at the γ-methyl C–H bonds through a more favorable five-membered palladacycle intermediate. The site of acetoxlylation of **1m** and **1n**, which contain both secondary γ-C(sp^3)–H bonds and unactivated primary β-C(sp^3)–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(sp^3)–H bond and secondary γ-C(sp^3)–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(sp^3)–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.

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, **mono2a** 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 **mono2a**. After basification of the aqueous solution, followed by extraction by organic solvent (DCM), the free amino alcohol was obtained in 80% yield.

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



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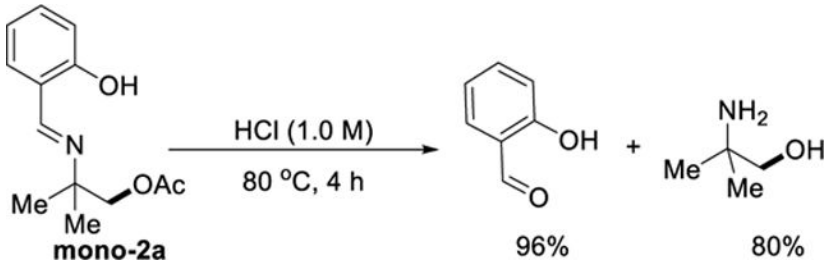
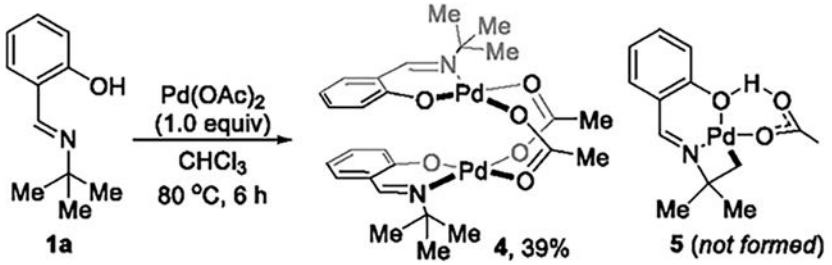


(3)

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



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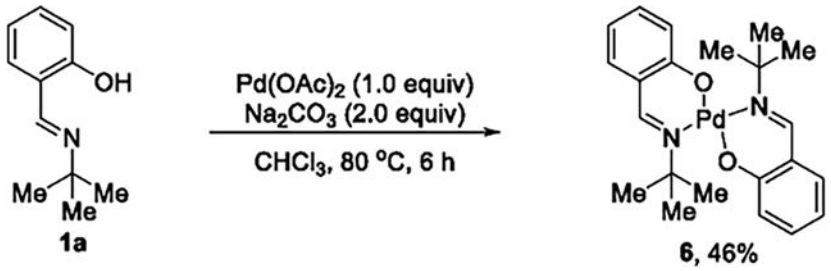

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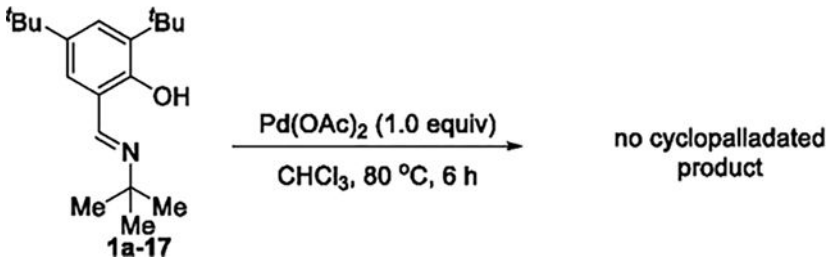
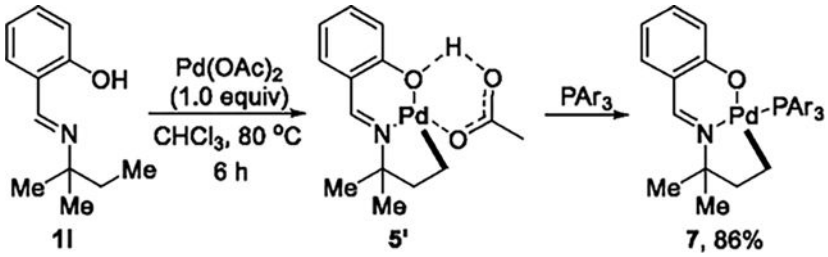


(6)

reaction in the presence of base (e.g., Na_2CO_3) to promote the C–H bond cleavage formed the palladium complex **6** containing two deprotonated salicaldimines, 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 (eq 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 $C(sp^3)$–H bond. Consistent with these synthetic studies, no palladacyclic intermediate was observed during the catalytic reactions (eqs 4–6), as judged by analysis of the crude reaction mixture by ^1H NMR spectroscopy. This set of mechanistic experiments suggests that the formation of the four-membered palladacycle is unfavorable and could lie uphill from the salicylaldimine complex **4**.

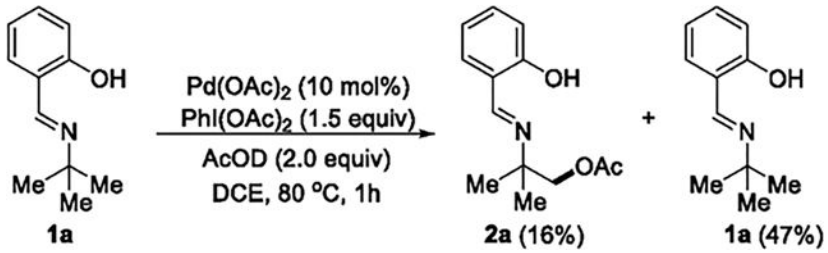
To test if a salicylaldimine-ligated palladium is capable of forming a metallacycle by cleavage of a $C(sp^3)$–H bond, we allowed $Pd(OAc)_2$ to react with substrate **1l** that could form a five-membered palladacycle under the same conditions as the reaction with **1a**. Indeed, the five-membered palladium 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 it by various methods. Thus, an external ligand (3,5-bis(trifluoromethyl)-



(7)

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).

To probe whether the β-C(sp^3)–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), ^{1}H NMR analysis of the crude reaction mixture



(8)

showed that 47% of the starting material **1a** remained (16% of the acetoxylated product **2a** formed), and no deuterium had been incorporated into the unreacted **1a**, as determined by ^{2}H 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

(9)

reaction of **5′** with 2 equiv of $PhI(OAc)_2$ occurred to completion at room temperature in less than 5 min to form the C-acetoxylated 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.

Density Functional Theory (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 salicaldimine by a concerted metalation–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 salicaldimine 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 that of 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 the monomeric salicaldimine complex **9** by 1.3 kcal/mol and uphill of the isolated dimeric analogue **4** by 10.6 kcal/mol, whereas formation of the five-membered pallacycle **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 $PhI(OAc)_2$ 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 acetoxylated products **8** and **8′** in which the functionalized salicaldimine 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 and 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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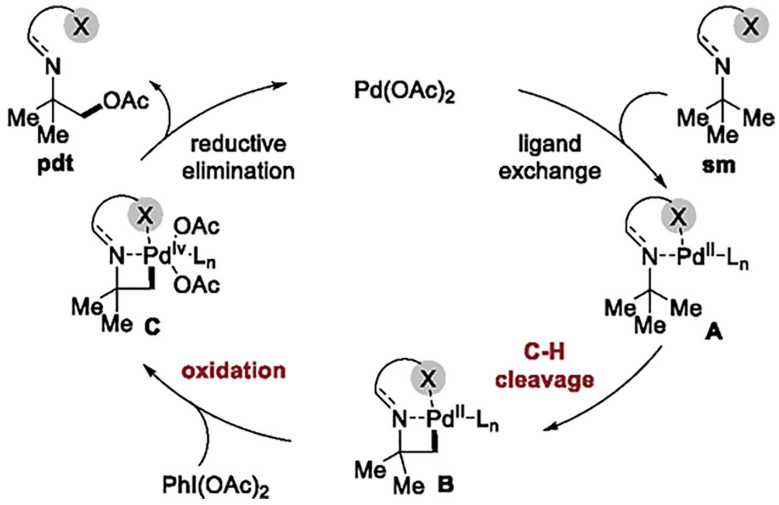


Figure 1.
Proposed catalytic cycle for the β-C–H functionalization

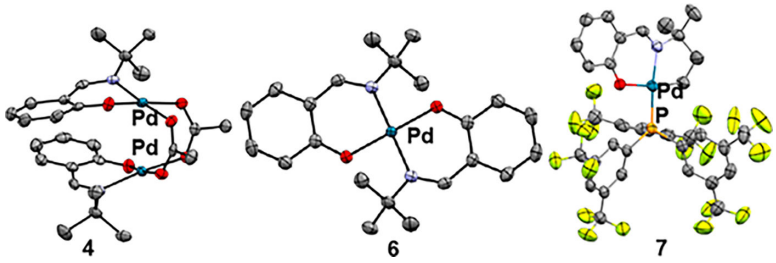


Figure 2.
Solid-state structures of **4, 5,** and **7** determined by single crystal X-ray diffraction.

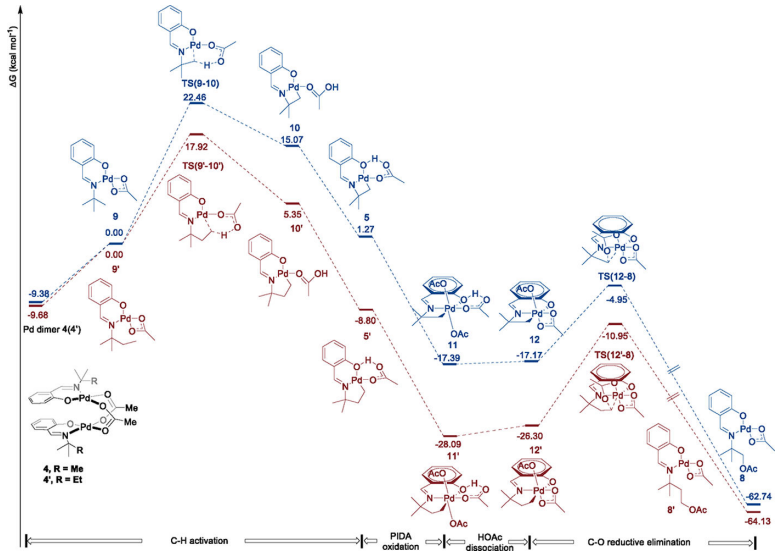
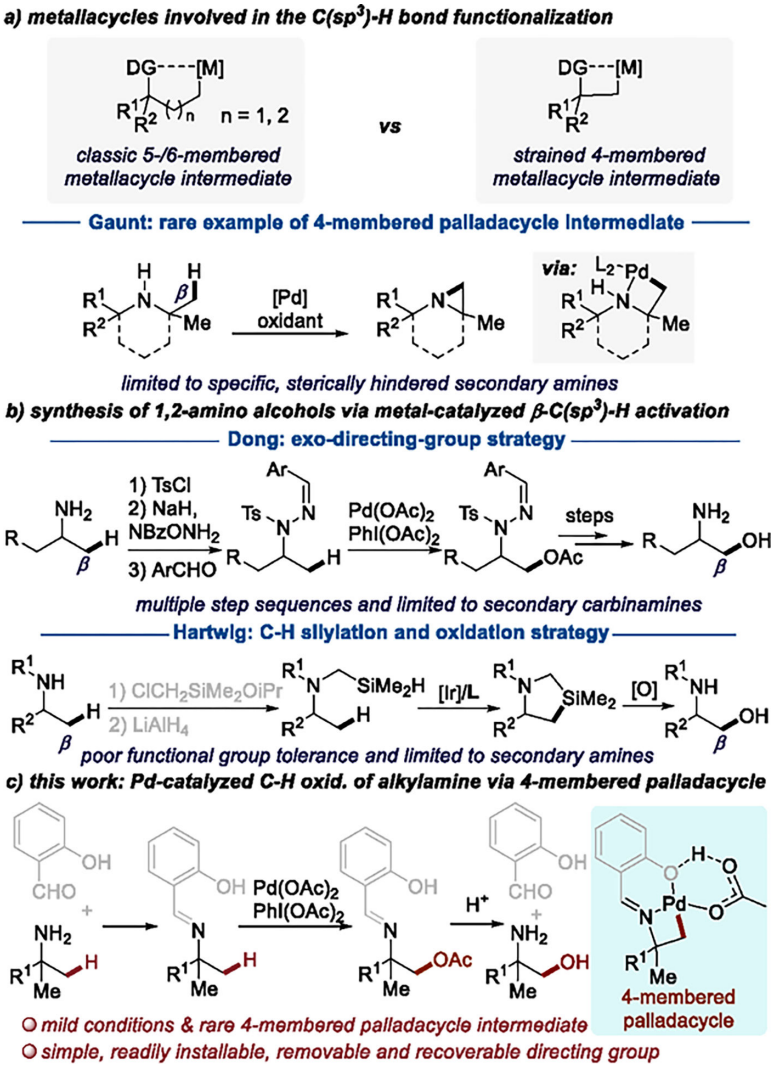


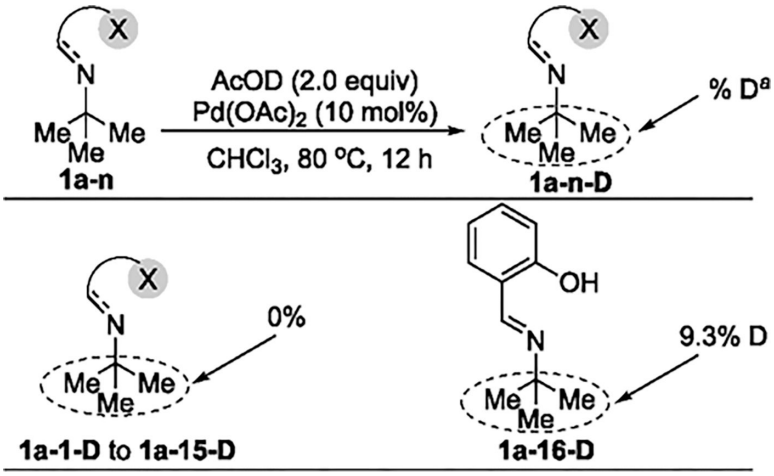
Figure 3.

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.



Scheme 1.

Transition-Metal-Catalyzed C–H Functionalization of Aliphatic Amines



Scheme 2.
H/D Exchange Experiments

Table 1.

Pd-Catalyzed C−H Acetoxylation of Amine Derivatives

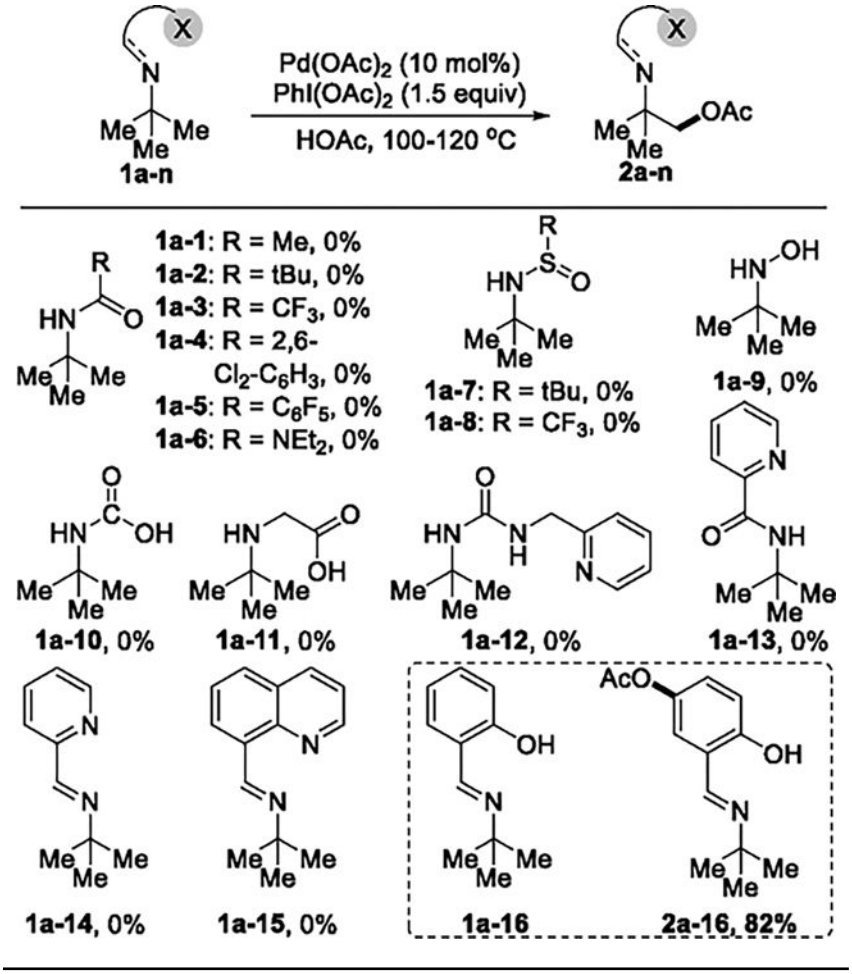
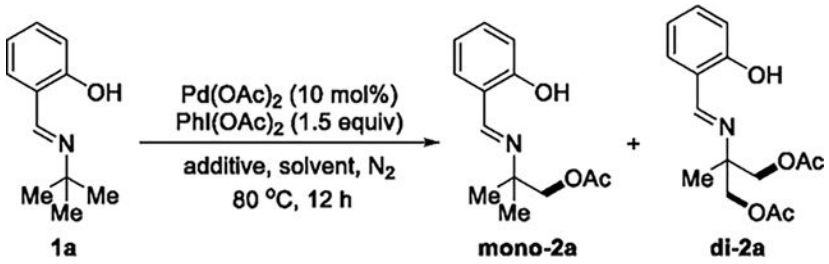


Table 2.

Evaluation of the Conditions for the Acetoxylation of Compound 1a[a]



1a mono-2a di-2a

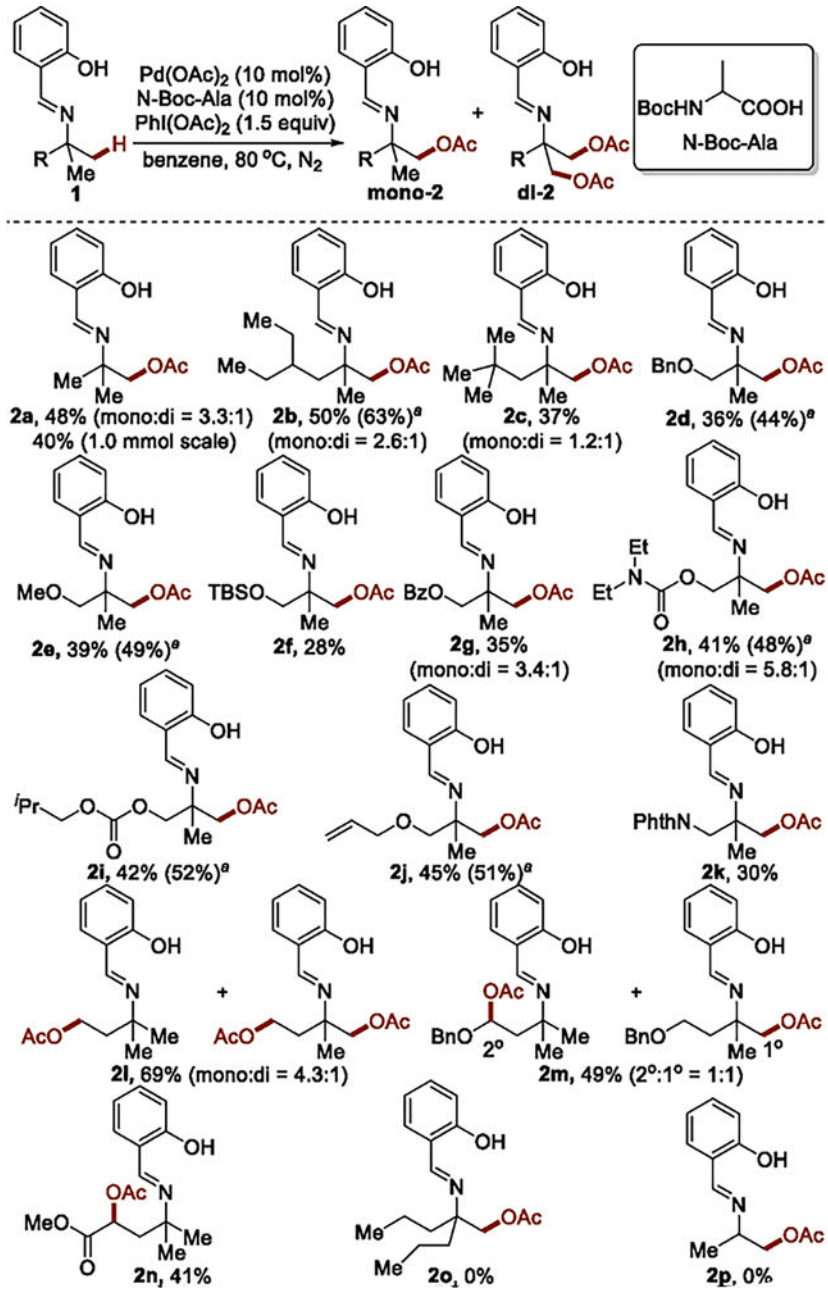
entry	additive	solvent	2a%	mono:di
1	NaOAc (1.5 equiv)	$CHCl_3$	48%	2.2:1
2	NaOAc (1.5 equiv)	*m*-xylene	34%	8:1
3	NaOAc (1.5 equiv)	benzene	51%	4:1
4	NaOAc (1.5 equiv)	toluene	34%	10:1
5	NaOAc (1.5 equiv)	THF	7%	>20:1
6	NaOAc (1.5 equiv)	dioxane	14%	>20:1
7	NaOAc (1.5 equiv)	EA	28%	8:1
8	NaOAc (1.5 equiv)	MeCN	25%	7:1
9	NaOAc (1.5 equiv)	DMF	4%	>20:1
10	NaOAc (1.5 equiv)	DMPU	0%	
11	Na_2HPO_4 (1.5 equiv)	benzene	48%	3.8:1
12	KH_2PO_4 (1.5 equiv)	benzene	49%	4:1
13	$PhSO_3Na$ (1.5 equiv)	benzene	51%	4:1
14	—	benzene	48%	4:1
15	N-Boc-Ala (10 mol %)	benzene	58%	4:1

[a]Conditions: Reaction was conducted with **1a** (0.1 mmol), Pd(OAc)2 (10 mmol %), and Phl(OAc)2 (1.5 equiv) in solvent (1.0 mL) at 80 °C under N_2; the yields and ratio of **mono2a** vs **di2a** were determined by gas chromatography (GC) with dodacane as the internal standard.

Abbreviations: ethyl acetate, EA; dimethylformamide, DMF; *N,N'*-dimethylpropyleneurea, DMPU.

Table 3.

Scope of the β-Acetoxylation of Amine Derivatives[a]



[a]The yields refer to isolated yields, and the yields in parentheses refer to yields based on recovered starting material.