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Communication

Ligand-Enabled γ-C(sp^3)−H Hydroxylation of Free Amines with Aqueous Hydrogen Peroxide

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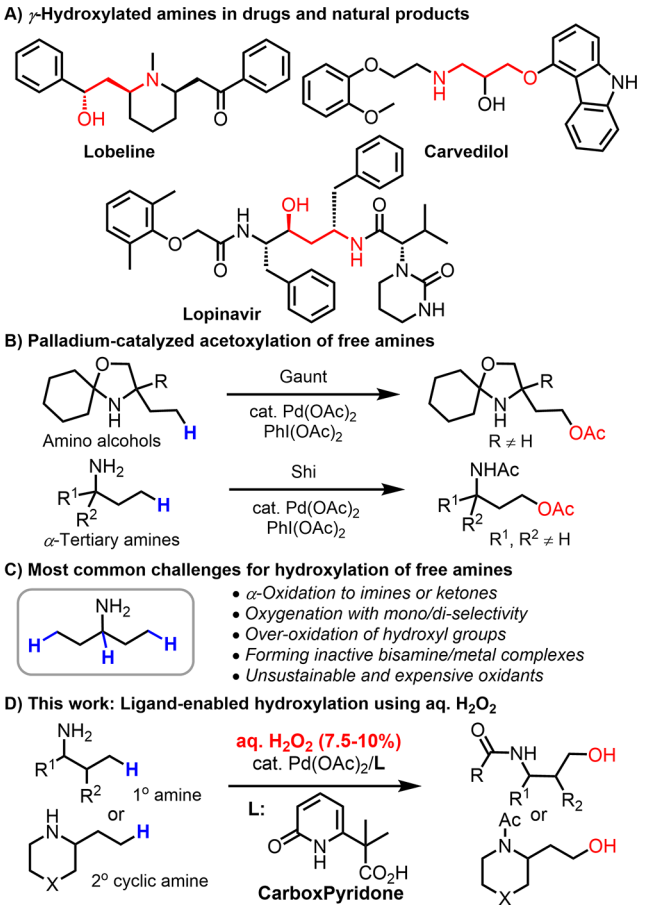
ABSTRACT: Selective oxidation of the γ-C−H bonds from abundant amine feedstocks via palladium catalysis is a valuable transformation in synthesis and medicinal chemistry. Despite advances on this topic in the past decade, there remain two significant limitations: C−H activation of aliphatic amines requires an exogenous directing group except for sterically hindered α-tertiary amines, and a practical catalytic system for C(sp^3)−H hydroxylation using a green oxidant, such as oxygen or aqueous hydrogen peroxide, has not been developed to date. Herein, we report a ligand-enabled selective γ-C(sp^3)−H hydroxylation using sustainable aqueous hydrogen peroxide (7.5−10%, w/w). Enabled by a CarboxPyridone ligand, a series of primary amines (1°), piperidines, and morpholines (2°) were hydroxylated at the γ-position with excellent monoselectivity. This method provides an avenue for the synthesis of a wide range of amines, including γ-amino alcohols, β-amino acids, and azetidines. The retention of chirality in the reaction allows rapid access to chiral amines starting from the abundant chiral amine pool.

Scheme 1. Pd(II)-Catalyzed γ-C−H Oxygenation of Amines



γ-Hydroxylated amines are not only common motifs in pharmaceuticals and natural products (Scheme 1A), but also versatile building blocks for organic syntheses.[1] Considering the abundant amine feedstocks and ready availability of chiral amines through established asymmetric methodologies,[2] the development of Pd(II)-catalyzed γ-C−H oxygenation of aliphatic amines could provide a versatile synthetic access to diverse γ-hydroxylated amines.[3] However, the most common free amines are not compatible with Pd(II) catalysts because the α-hydrogen in amines is more susceptible to oxidation leading to imines or carbonyl compounds.[4] In addition, the formation of unreactive bis(amine) palladium complexes with amine substrate is also a major hurdle.[5] Except for C−H acyloxylation of using strongly coordinating directing groups[6,7] and transient directing groups,[8] free amine substrates are largely limited to bulky protected amino alcohols[9] or amines containing an α-quaternary center[10] (Scheme 1B). Notably, these catalytic reactions typically afford a mixture of mono- and diacetoxylated products. Therefore, a practical and general catalytic system for monoselective γ-C−H hydroxylation of free aliphatic amines remains elusive (Scheme 1C).

In addition to the difficulty associated with the C−H activation of free amines, identification of an environmentally friendly and sustainable oxidant for oxidatively sensitive amines is another formidable challenge. Although our first entry into Pd(II)-catalyzed C−H oxygenation reactions investigated the use of *tert*-butyl peroxide as the oxidant, success in using

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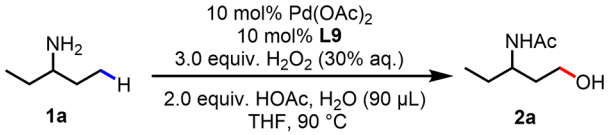
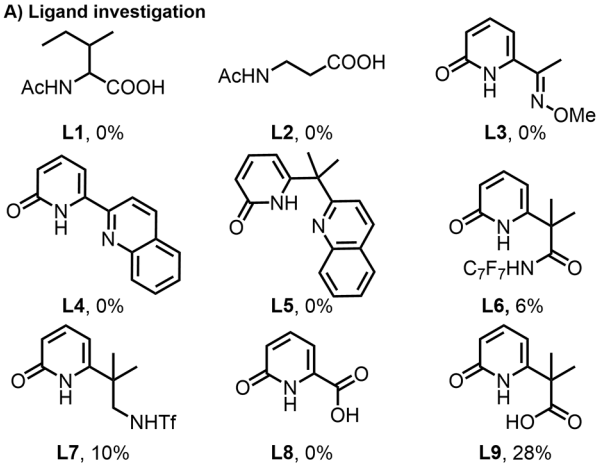
Table 1. Optimization of the C(sp^3)−H Hydroxylation of Free Amines[a,b]

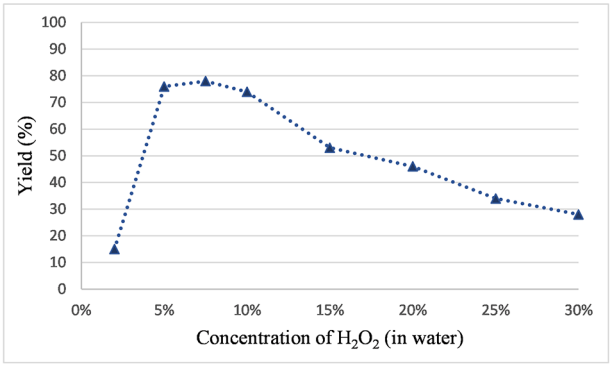


Entry	Conditions	Yield (%)
1	w/o $Pd(OAc)_2$ or ligand	0
2	**L1-L9**	see **A**
3	concentration of aq. H_2O_2	see **B**
4	$PhI(OAc)_2$ instead of H_2O_2	0
5	DMF, DCE, CH_3CN instead of THF	45, 26, 26
6	70 °C or 110 °C	45, 70
7	acids	see **C**

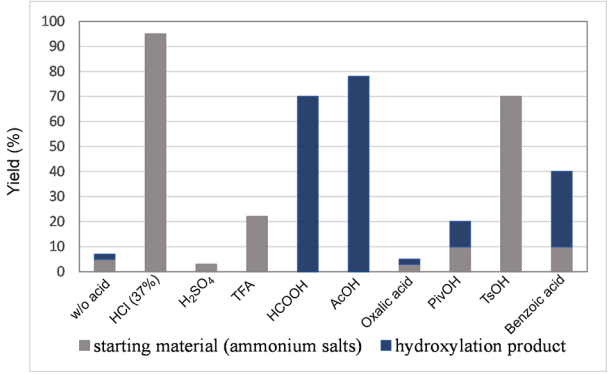
A) Ligand investigation



B) Concentration of hydrogen peroxide investigation



C) Acid investigation



[a]Conditions: **1a** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), ligand (10 mol %), acid (2.0 equiv), H_2O_2 (30% aqueous solution, 3.0 equiv), and H_2O (0−420 μL) in THF (0.6 mL), 90 °C, 12 h. [b]Yield was determined by ^{1}H NMR using CH_2Br_2 as the internal standard.

inexpensive peroxides largely requires installation of strongly coordinating directing groups.[11] In particular, unlike the biomimetic metal-oxo chemistry,[12] the sustainable and practical aqueous hydrogen peroxides are largely incompatible with transition metal catalysts; for example, rapid decomposition by Pd(II) catalysts was established in Wacker oxidation catalysis. The Vedernikov group showed that the arylpalladium(II) complex can be oxidized by hydrogen peroxide to give a hydroxo-palladium(IV) complex in the presence of di-2-pyridyl ketone ligand.[13] Through the development of bifunctional pyridine ligands, we have recently realized the first example of C(sp^2)−H hydroxylation of phenylacetic acids and benzoic acids using aqueous hydrogen peroxide.[14] Herein, we report an unprecedented C(sp^3)−H hydroxylation of a wide range of free amines using aqueous hydrogen peroxide (7.5−10%, w/w) as the sole oxidant (Scheme 1D). The use of a bifunctional carboxyl-pyridine ligand is essential for this reaction to proceed. The one-pot formation of γ-amino alcohols with the amino group monoselectively protected allows subsequent synthetic elaborations. Valuable β-amino acids and azetidines are also prepared using these γ-amino alcohol intermediates.

Our exploratory study on γ-C(sp^3)−H oxygenation of free amines commenced with 3-aminopentane (**1a**) as a representative substrate (Table 1). No desired product was obtained in the absence of a ligand (entry 1). The essential role of bifunctional ligands in enabling Pd(II)-catalyzed C−H activation reactions prompted us to focus on ligand development for this proposed transformation (entry 2, Table 1A).[15] However, our early bifunctional monoprotected amino acid (MPAA) ligands, including the α-amino acid ligand (**L1**) and β-amino acid ligand (**L2**), were not effective for this reaction. Building on the success that pyridone-based bidentate ligands could promote C(sp^3)−H functionalization of carboxylic acids, a wide range of bifunctional ligands, such as oxime ether-pyridone (**L3**),[16a] pyridine-pyridone (**L4**, **L5**),[16b,c] amide-pyridone (**L6**),[16d] and sulfonamide-pyridone (**L7**),[16e] were investigated for the oxidation of free amines. While these ligands exhibited poor activity in the reaction, we could obtain a small amount of desired hydroxylated product using X,X-type ligands (**L6**, 6%; **L7**, 10%). We then turned our attention to another important X,X-type ligand (CarboxPyridone), which was shown to promote C(sp^2)−H hydroxylation of phenylacetic acids and benzoic acids using aqueous hydrogen peroxide as the sole oxidant.[14] Excitingly, six-membered chelating **L9** emerged as the most promising ligand for the γ-C−H hydroxylation of free amines, which affords the oxygenated product in 28% NMR yield. Interestingly, the amino group was selectively protected with the free hydroxyl intact, which is synthetically desirable. While extensive modification of reaction conditions failed to improve the yield, we were delighted to find that adding more water to the reaction mixture to dilute lab-grade H_2O_2 (w/w, 30%) to 7.5% improved the yield to 78% (entry 3, Table 1B). The optimum

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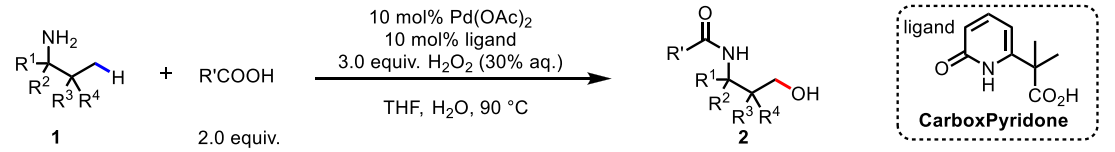
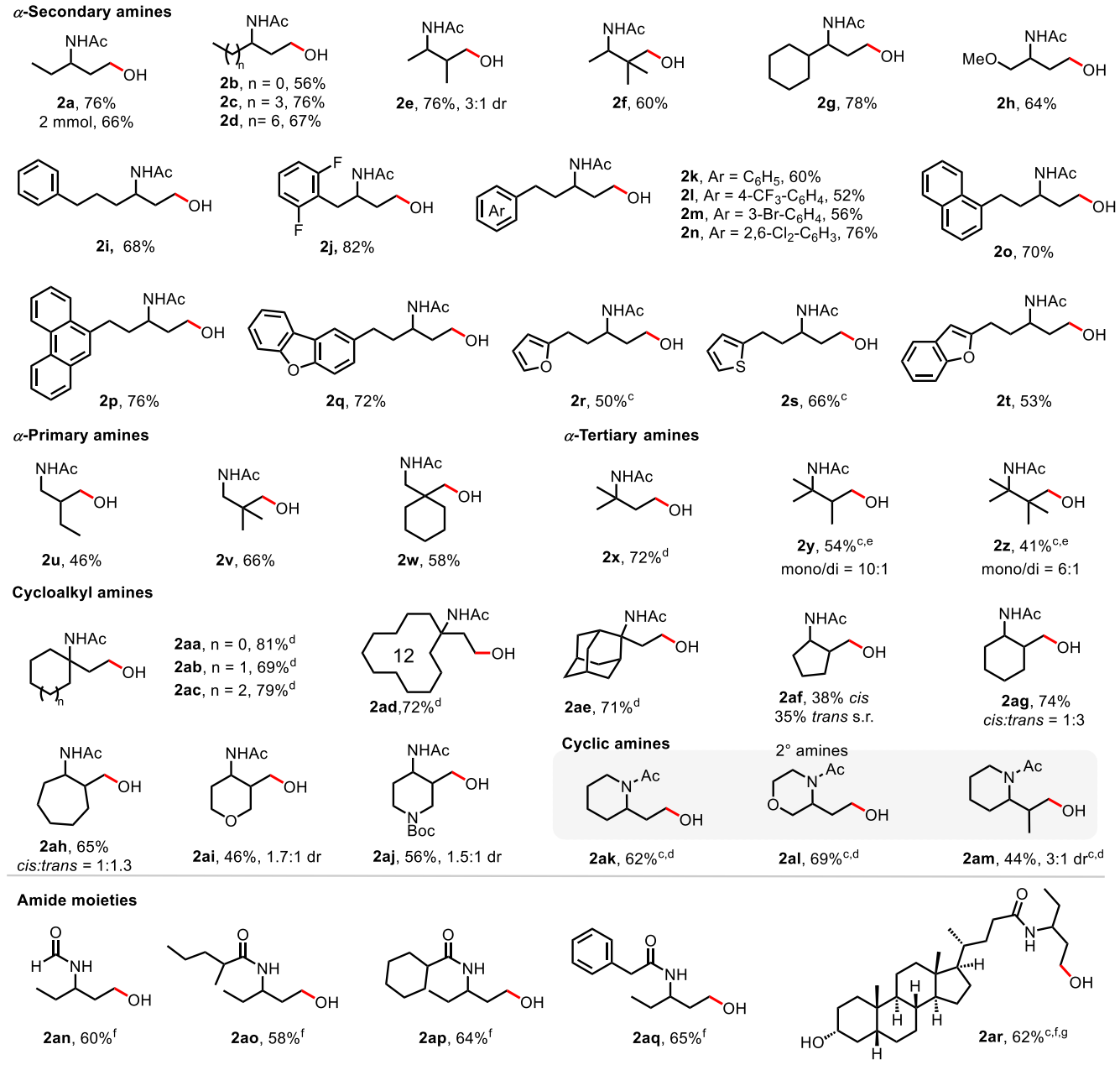
Table 2. Substrate Scope for the C(sp^3)–H Hydroxylation of Free Amines[a,b]





[a]Conditions: Amines **1a**–**1am** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), CarboxPyridone (10 mol %), acids (2.0 equiv), H_2O_2 (30% aqueous solution, 3.0 equiv), and H_2O (90 μL) in THF (0.6 mL), 90 °C, 12 h. [b]Isolated yields. [c]TBHP (*tert*-butyl hydroperoxide) (70% aqueous solution, 3.0 equiv) instead of H_2O_2. [d]H_2O (60 μL) in THF (0.9 mL). [e]Dioxane (0.6 mL) instead of THF, at 80 °C. [f]$Pd(CH_3CN)_4(BF_4)_2$ instead of $Pd(OAc)_2$. [g]Compound **1a** (0.15 mmol, 1.5 equiv) was used.

concentration of H_2O_2 is critical for the oxidation of alkyl-palladium intermediate, as well as prevention of the decomposition of H_2O_2. Other reaction parameters, including palladium catalyst, solvent, oxidizing agent, and temperature, were also screened to optimize this C–H hydroxylation reaction (entries 4–6 and Tables S3–S6). Since the presence of acid additive was found to be essential for this reaction to proceed, a series of inorganic and organic acids were tested, and the results showed that a number of acids can stabilize amines by effectively inhibiting α-oxidation (entry 7, Table 1C). However, only acetic and formic acids were found to be effective in promoting γ-C–H oxidation, which led to the formation of amine products protected by these acids.

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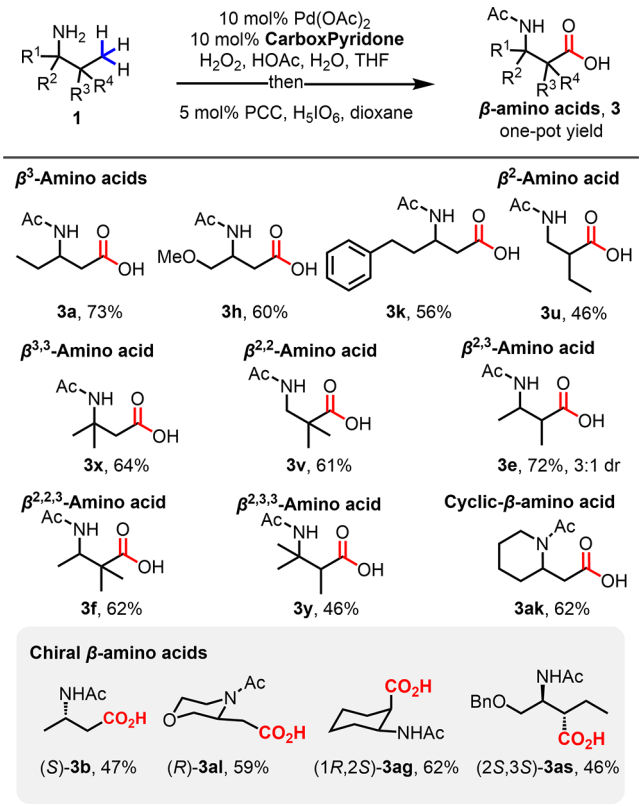
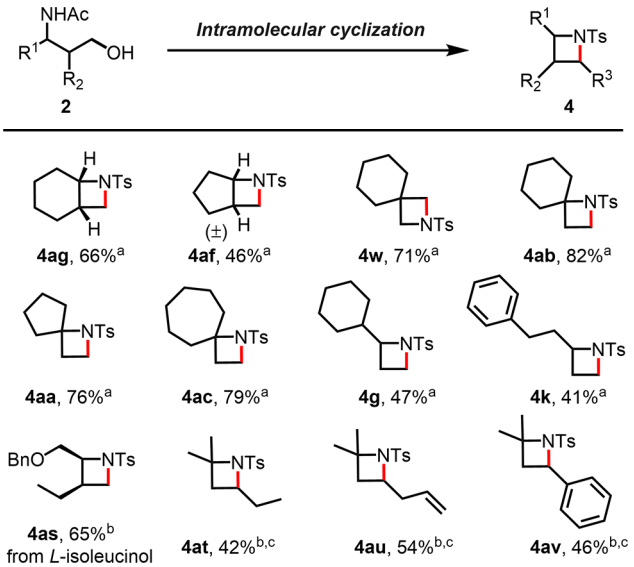
Table 3. One-Pot Synthesis of β-Amino Acids[a,b]



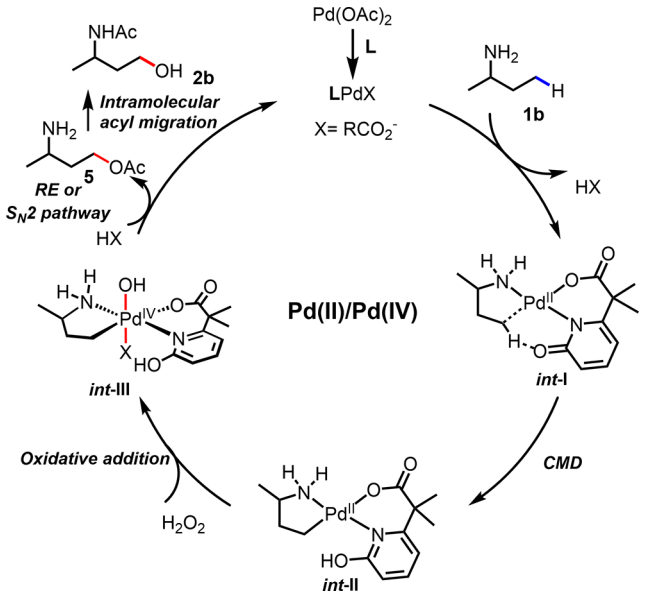
[a]The hydroxylation reaction was performed under conditions matching those outlined in Table 2. Upon completion of the reaction, the solvent was evaporated, and additional oxidation conditions were subsequently introduced: pyridinium chlorochromate (PCC) (5 mol %), H_5IO_6 (3.0 equiv) in 1,4-dioxane (1 mL), rt, 5 h. [b]Isolated yields.

Table 4. Synthesis of Azetidines



[a]Cyclization conditions: (1) HBr (48% aq), 100 °C, 6 h; (2) TsCl, Cs_2CO_3, CH_3CN, 90 °C, 24 h. [b]Cyclization conditions: (1) 1 M NaOH aq, EtOH, reflux; (2) TsCl, Et_3N, DCM, rt; (3) TsCl, KOH, THF, reflux. [c]Yields are based on the corresponding alcohols **2at**–**2av**. See the Supporting Information for the synthesis of secondary alcohols **2at**–**2av** from **2x**.

Scheme 2. Proposed Catalytic Cycle



Having determined optimal conditions, we subjected a wide range of commercially available amines to the hydroxylation reaction conditions (Table 2). α-Substituted amines with short alkyl chains (**2a**, **2b**, **2e**, and **2f**) and long alkyl chains (**2c**, **2d**), as well as cycloalkyl (**2g**) and heteroalkyl (**2h**) substituents, afforded the hydroxylated products in good yields. Furthermore, various aryl groups (**2i**–**2n**) were found to be compatible without benzyl oxidation. Other aromatic rings, such as naphthalene (**2o**), phenanthrene (**2p**), dibenzofuran (**2q**), furan (**2r**), thiophene (**2s**), and benzofuran (**2t**), were also well tolerated to give good to high yields. The versatility of this method was demonstrated with both α-primary (**2u**–**2w**) and α-tertiary amines (**2x**–**2z**). Cycloalkylamines with 5-membered (**2aa**), 6-membered (**2ab**), and 7-membered (**2ac**) rings, as well as 12-membered (**2ad**) and adamantane (**2ae**) rings, were all suitable substrates that afforded good yields (69–81%). Hydroxylation of the mixture of *cis*- and *trans*-cyclopentylamine (**2af**) gave the *cis*-hydroxylated product in 38% yield, with no *trans*-hydroxylated product formed and 35% of the *trans*-cyclopentylamine retained. In contrast, both *cis*- and *trans*-amines with 6- and 7-membered rings were hydroxylated to give a mixture of diastereomers in 74% and 65% yield, respectively (**2ag**, **2ah**). Notably, saturated heterocycles, such as tetrahydropyran and piperidine, were also compatible, and gave the desired product in moderate yields (**2ai**, **2aj**). Moreover, the secondary nitrogen on the piperidine and morpholine rings could direct C–H hydroxylation to give the products in good yields (**2ak**–**2am**). The amide moieties could also be diversified by replacing the acetic acid with other carboxylic acids (**2an**–**2ar**).

Asymmetric synthesis of optically pure diverse β-amino acids remains a significant task.[17] We envisaged that our oxygenation strategy, combined with subsequent oxidation of the hydroxyl group (for screening conditions, see Table S7), could provide a versatile platform for the synthesis of β-amino acids from a wide range of readily available chiral amines (Table 3). By utilizing a one-pot approach, β^3-amino acids (**3a**, **3h**, **3k**), β^2-amino acid (**3u**), $\beta^{3,3}$-amino acid (**3x**), $\beta^{2,2}$-amino acid (**3v**), $\beta^{2,3}$-amino acid (**3e**), $\beta^{2,2,3}$-amino acid (**3f**), $\beta^{2,3,3}$-amino acid (**3y**), and cyclic β-amino acid (**3ak**) could be obtained in good

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to high yields. Various chiral amines were also converted to optically pure chiral β-amino acids in one pot (**3b**, **3al**, **3ag**, **3as**).

In light of the importance of azetidines in drug discovery,[18] we investigated the feasibility of converting the hydroxylated amine products into azetidines via cyclization (Table 4). Amino alcohols could be readily deprotected and brominated in a hydrobromic acid solution, followed by ring closure in the presence of TsCl and Cs_2CO_3. This one-pot synthesis offered a convenient method for the preparation of diverse azetidines, including fused bicyclic (**4ag**, **4af**) and spiro bicyclic (**4w**, **4aa**−**4ac**). Commercially available L-isoleucinol was also successfully converted to chiral azetidine using this approach (**4as**). The initially formed primary alcohols could be effectively converted to the secondary alcohols (**2at**−**2av**) in good yields (65−72%, see the Supporting Information). These amino alcohols were also compatible with the cyclization protocol, thereby further broadening the range of azetidines (**4at**−**4av**).

The formation of the monoprotected amino alcohols is intriguing. To gain further insights into this reaction, we conducted several control experiments (Figure S5). First, we observed that the acetyl-protected amine did not yield any product under the standard conditions, thereby suggesting that the active substrate involved in the C−H activation is a nonprotected amine. Second, free amino alcohols remain intact without any protection under the standard reaction conditions. Instead, the *O*-acetyl amino alcohol **5** was readily converted into the acetyl-protected amine **2b** as the desired product. These observations suggest that C−H acetoxylation occurs initially, followed by a subsequent acetyl migration step leading to the formation of the monoprotected amino alcohols.[19] On the basis of these studies, a Pd(II)/Pd(IV) catalytic cycle is proposed (Scheme 2).[11,14] The coordination of the Carbox-Pyridone ligand with the palladium catalyst generates the active catalyst. Following ligand-enabled C−H cleavage through the concerted metalation−deprotonation (CMD) mechanism, oxidative addition of H_2O_2 to Pd(II) forms the high-valent Pd(IV) species. Subsequently, the Pd(IV) species undergoes reductive elimination or an S_N2-type reaction to result in the formation of an acyloxylated intermediate **5**, which subsequently undergoes acetyl migration to give amino alcohol products.

In summary, we have developed Pd(II)-catalyzed monoselective C(sp^3)−H hydroxylation of primary amines, piperidines, and morpholines using aqueous hydrogen peroxide as a green oxidant. Notably, this method also allows one-pot synthesis of monoprotected γ-amino alcohols. The success of this reaction critically hinges upon the presence of the CarboxPyridone ligand, which prevents the formation of the unreactive bis(amine) palladium complex and promotes the oxidation of the alkyl-palladium intermediate by hydrogen peroxide for the hydroxylation step to proceed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c09340.

Full experimental details and characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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