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Ligand-Enabled C—H Hydroxylation with Aqueous H_2O_2 at Room Temperature

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Abstract

With the large number of Pd(II)-catalyzed C—H activation reactions of native substrates developed in the past decade, the development of catalysts to enable the use of green oxidants under safe and practical conditions has become an increasingly important challenge. Notably, the compatibility of Pd(II) catalysts with sustainable aqueous H_2O_2 has been a long standing challenge in catalysis including Wacker-type oxidations. We report herein a bifunctional bidentate carboxyl-pyridone (CarboxPyridone) ligand that enables room-temperature Pd-catalyzed C—H hydroxylation of a broad range of benzoic and phenylacetic acids with an industry-compatible oxidant, aqueous hydrogen peroxide (35% H_2O_2). The scalability of this methodology is demonstrated by a 1000 mmol scale reaction of ibuprofen (206 g) using only a 1 mol% Pd catalyst loading. The utility of this protocol is further illustrated through derivatization of the products and synthesis of polyfluorinated natural product coumasten and pterocarpene from phenol intermediates prepared using this methodology.

Graphical Abstract

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Supporting Information The Supporting Information is available free of charge on the ACS Publications website. Full experimental details and characterization of new compounds (PDF)

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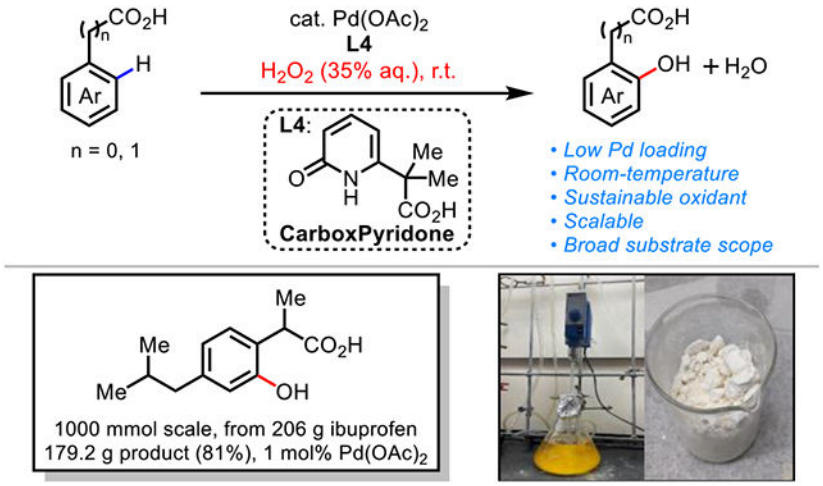

1. Introduction

Phenols are not only common motifs in natural products and bioactive compounds (Scheme 1a),[1] but also versatile building blocks for organic syntheses.[2] Accordingly, a variety of approaches have been developed to access this important motif, including chemical synthesis,[3] biochemical synthesis[4] and the controlled decomposition of natural compounds,[5] such as lignin depolymerization. Modern transition metal catalysis has made significant advances in converting a variety of aryl halides or aryl boronic acids into phenols.[6] In principle, the direct hydroxylation of aryl C—H bonds offers an appealing, single-step alternative, but the realization of this strategy has proven challenging. Various strategies ranging from photocatalytic methods[7a,7b] to nickel,[7c] manganese,[7d] copper,[7e] and iron[7f,7g] catalysis have been explored to achieve aromatic C—H oxidations. Recently, palladium catalysis has emerged as a powerful strategy for selective oxygenation of C—H bonds.[8,9] The C—H hydroxylation reactions of arenes bearing strongly coordinating directing groups such as pyridyl or oxime have been reported using various oxidants,[8a-f] however, these substrates are not practical for the synthesis. There are a handful of examples on C(sp^2)—H oxidation directed by weakly coordinating native directing groups such as free carboxylic acids using hypervalent iodine reagents such as $PhI(OAc)_2$, and an additional hydrolysis step is required to access the final phenolic compound (Scheme 1b).[9f,9g]

In order for C—H hydroxylation to be practical and scalable, it is essential that methodologies employ a cheap and environmentally friendly oxidant. Recently we demonstrated the feasibility of using molecular oxygen for the direct hydroxylation of C—H bonds of (hetero)benzoic acids (Scheme 1c),[10] however, the efficiency, scope, and safety of pure oxygen are unsuitable for industrial scale applications. Since aqueous H_2O_2 has been used in several landmark ton-scale industrial processes including the HPPO (converting propene to propylene oxide) and ε-Caprolactam processes,[11] we envisioned that Pd-catalyzed C—H hydroxylation with H_2O_2 could provide a practical solution to the synthesis of phenols. However, hydrogen peroxide tends to decompose under the elevated temperature generally required for previously reported Pd(II)-catalyzed C—H activation reactions. Herein we report the development of a bifunctional bidentate carboxyl-pyridone

(CarboxPyridone) ligand that enables room-temperature C(sp^2)—H hydroxylation of native carboxylic acid substrates with practical, aqueous H_2O_2 as the sole oxidant (Scheme 1d). This new protocol provides an efficient synthetic route to access a wide range of phenols, the synthetic utility of which was demonstrated through the synthesis of two polyfluorinated natural products. Importantly, the reaction can be efficiently scaled up, as highlighted by the synthesis of 179 grams of *ortho*-hydroxylated ibuprofen. Preliminary mechanistic studies demonstrate that ligand is crucial for accelerating C—H cleavage at room temperature, which prevent the decomposition of hydrogen peroxide.

2. Results and Discussion

Itoh et al. has reported Pd(II) catalyzed the strongly coordinating pyridine directed C(sp^2)—H hydroxylation using hydrogen peroxide.[8e] Given our goal of developing a practical C—H hydroxylation reaction, we were interested in developing C—H hydroxylation directed by common, weakly coordinating native directing groups. We were particularly interested in carboxylic acid directing groups due to the abundant sources and versatile conversions. We began our investigation of C(sp^2)—H hydroxylation using 4-trifluorometylphenylacetic acid (**1a**) as a model substrate with 2 mol% $Pd(OAc)_2$ loading at a 1.0 mmol scale (Table 1). Mono *N*-protected amino acid ligand (MPAA) **L1** was chosen for preliminary screening as this ligand is known to accelerate C—H bond cleavage with phenyl acetic acid substrates by direct participation of the acetylamino motif (NHAc) as an internal base during the concerted metalation-deprotonation (CMD) step.[12] To our delight, **L1** enabled the formation of the desired *ortho*-hydroxylated product **2a** in 37% yield when using N,N-dimethylacetamide (DMA) as the solvent and H_2O_2 (35% aq.) as the oxidant at 90 °C (entry 1). Experiments show that Pd(II) salts decompose 85% of the H_2O_2 at 90 °C within 20 min (see Supporting Information). We reasoned that the key to improve this reaction is to find a ligand that can ensure Pd(II) catalyst activates C—H preferentially than H_2O_2. Although the decomposition of H_2O_2 was not observed under the reaction conditions at room temperature, MPAA ligands **L1** and **L2** proved incapable of enabling C—H hydroxylation at room temperature (entries 2-3). Therefore, it was crucial to develop a new ligand that would enable C—H activation at room temperature. Recently, 2-pyridones have emerged as particularly effective ligands that play analogous role to NHAc for challenging Pd(II) catalyzed C—H activation reactions.[10,13] We hypothesized that incorporation of the 2-pyridone group into the MPAA scaffold in place of NHAc might enable the C—H activation at mild reaction temperatures. Consequently, we designed and tested the pyridone-containing MPAA analogs **L3** and **L4 (CarboxPyridone).** While the five membered chelate **L3** did not afford the desired product (entry 4); surprisingly, the six-membered chelate **L4** afforded **2a** in a 65% yield under the room temperature conditions (entry 5). We propose that the increased flexibility of the six-membered chelate may compensate for the rigidity of the planar 2-pyridone motif, allowing the ligand to adopt a favorable conformation for pyridone-assisted C—H cleavage step. When monodentate 2-pyridone ligand **L5** and **L6** are applied, only trace amount of product was observed, demonstrating the importance of bidentate nature of the ligand (entries 6-7). Interestingly, **L7** and **L8**, two recently developed effective bidentate pyridone-pyridine ligands for C—H activation reactions were not effective (entries 8-9),[13] indicating the importance of retaining

a carboxylic acid motif in the bidentate ligand. A control experiment without ligand clearly indicates that ligand plays a key role for this reaction (entry 10). Further optimization with **L4** revealed that the base and solvent combinations of KHCO3 with DMA (entry 11) and K_2HPO_4 with CH_3CN (entry 12) afforded the product in excellent yields (see Supporting Information for screening details).

Having determined optimal conditions, we subjected a wide range of phenylacetic acids to the hydroxylation reaction (Table 2). Phenylacetic acids containing electron-withdrawing (**1a, 1e-1k**) or electron-donating (**1b, 1c**)*para*-substituents, as well as un-substituted (**1d**) all provided the corresponding products in high yields. Substrates with various substitution patterns (**1l-1q**) were also smoothly hydroxylated in high yields, affording the hydroxylated products at the less hindered positions. In addition, the α-substituents of carboxylic acids (**1r-1u**) were also tolerated, generating the corresponding hydroxylated products. It is noteworthy that hydroxylations of biologically active molecules such as mandelic acids (**1v, 1w**), protected phenylglycine (**1x**) and tropic acid (**1y**) were feasible providing expedient access to phenol derivatives. The phenylacetic acids with tetralin skeleton (**1z**), dibenzofuran (**1aa**) and α-quaternary centers (**1ab-1ad**) were also compatible. Interestingly, the reactions are highly selective for C(sp^2)—H bonds, leaving potentially reactive cyclopropyl β-C(sp^3)—H bonds intact (**2ac, 2ad**). Late-stage modification of the existing drug molecules is a powerful approach to rapidly optimize bioactivity of lead compounds. Various anti-inflammatory drugs such as ibuprofen (**1ae**), ketoprofen (**1af**), flurbiprofen (**1ag**), loxoprofen (**1ai**), and naproxen (**1aj**) were all successfully hydroxylated with the new practical method. Other pharmaceuticals, including actarit (**1ah**) and itanapraced (**1ak**), were also hydroxylated in high yields and with high regioselectivity. Likewise, the complex phenylacetic acid derived from estrone (**1al**) was hydroxylated at the *ortho*-position in good yield.

Our discovery of ligand-enabled C(sp^2)—H hydroxylation of phenylacetic acid substrates led us to test whether this methodology is also applicable to another important class of substrates, benzoic acids (Table 3). It is worth noting that a single catalyst is often not compatible with both phenylacetic acid and benzoic acid scaffolds. To our delight, salicylic acid (**4a**) was obtained in high yield when benzoic acid was subjected to the similar conditions, differing only in the use of potassium phosphate dibasic trihydrate (K_2HPO_4•$3H_2O$) as the base. Alkyl or aryl substituted benzoic acids (**3b-3f**) were effective substrates, affording the corresponding mono-hydroxylated products in good to excellent yields. The reaction was selective for C(sp^2)—H hydroxylation with substrate **3d**, for which monodentate 2-pyridone ligands have previously been reported to effect benzylic C(sp^3)—H activation.[14] 1-Naphthoic acid (**3g**) was successfully hydroxylated on 2-position under the reaction conditions without decarboxylation.[8g] A higher temperature of 60 °C was required for substrate with electron-withdrawing trifluoromethyl group to achieve good yield (**3h**). Apparently, no significant H_2O_2 decomposition occurred at this relatively mild temperature. Methoxy and cyclic ether substituted benzoic acids (**3i-3k**) were also compatible substrates. For dihydrobenzofuran carboxylic acid substrate **3j**, both regioisomers were obtained in 1:1 ratio (**4j** and **4j'**). NSAID compound diflunisal (**4l**) could be synthesized from corresponding benzoic acid (**3l**). However, only trace amount of product was observed for the attempted

reaction of 2,4-difluorobenzoic acid (**3m**). With modified conditions, 2,4-difluorobenzoic acid (**3m**) was hydroxylated in 72% yield by increasing the $Pd(OAc)_2$ loading to 5%, and switching solvent to DMA. These new reaction conditions (Conditions B) were then applied to more substrates. We performed high yielding *ortho*-hydroxylations of benzoic acids with various substituents such as difluoro (**3m-3o**), fluoro (**3p**), nitro (**3q**), acetyl (**3r**), methoxy (**3s**) and 4-toluoyl (**3u**) groups. An *ortho*-bromo group remained intact during the selective $C(sp^2)$—H hydroxylation of substrate **3t**. A hydroxy group was introduced successfully to NSAID drug tolfenamic acid (**3v**). Estrone derived benzoic acid compound **3w** was also hydroxylated in 61% yield.

The robustness and scalability of the hydroxylation reaction was demonstrated through the large-scale reactions of several substrates (Scheme 2a). A mole-scale (206 g) reaction of ibuprofen at room temperature resulted in the formation of 179.2 g of **2ae** (81% yield) even with lower loading of 1 mol% $Pd(OAc)_2$. Similarly, large-scale reactions of **1a** and **1d** exhibited good yields. The hydroxylation of benzoic acids also proved to be highly scalable, with an 100 mmol scale reaction of benzoic acid (**3a**) affording 10.6 g of product **4a** (77% yield). These results show the potential of this methodology in industrial processes. To showcase the synthetic utility of the reaction, the carboxyl acid directing group of the hydroxylated products were derivatized to various functional groups (Scheme 2b). 2-Hydroxy phenylacetic acids (**2a** and **2d**) could be converted to the corresponding lactones (**5a, 5b**) and hydrobenzofurans (**5c, 5d**) through cyclization. Carboxylic acid directing groups were transformed to heterocycles such as the oxazoline (**5e**) and the benzimidazole (**5f**). In addition, we sought to demonstrate the utility of the hydroxylation reaction through the synthesis of analogs of natural products. The coumestans and pterocarpans are found in nature, some of which have significant biological activities.[15] Since the presence of fluorine substituent can uniquely impact the biological and physical properties of compounds, we embarked on the synthesis of unnatural fluorinated coumestan and pterocarpan using building blocks prepared from the title $C(sp^2)$—H hydroxylation reaction (Scheme 2c). The fluorinated precursors **2i** and **4m** were synthesized in one step from the commercially available carboxylic acids. Salicyl aldehyde **6** was synthesized from **4m** in 2 steps. A Perkin reaction of **2h** and **6** followed by oxidation afforded trifluorinated coumestan derivative **7** in good yield. We were also able to prepare the trifluorinated version of pterocarpene **8** by reduction of **7** followed by ring closure.

Preliminary mechanistic studies were conducted to gain further insight into the roles of the reaction components. A deuterium labeling experiments of **1d** with D_2O in the presence of **L4** or **L8** resulted in deuterium incorporation into the *ortho*-positions. However, in the presence of MPAA **L1** or in the absence of ligand, H/D exchange was not observed (Scheme 3a). These results suggest that the CMD active 2-pyridone motif in bidentate ligands is critical for enabling room temperature C—H activation. The kinetic isotope effect (KIE) was measured through parallel experiments of **1d** and **1d**-d_5 (see Supporting Information for details). The measured k_H/k_D value of 1.08 suggests that C—H cleavage is fast and not the rate-limiting step (Scheme 3b). The palladacycle intermediate (**9**) prepared from 2-methyl benzoic acid was subjected to the hydroxylation conditions and provided the product in 51% yield, consistent with the proposal that palladacycles such as **9** are active

intermediates in the reaction (Scheme 3c). The kinetic experiments of the oxidation step with **14** and without ligand shows that PyriCarbox ligand can stabilize the C—H activation intermediate to ensure the smooth oxidation step with H_2O_2 (Figure S10). Based on these observations and previous reports,[16] a Pd(II)/Pd(IV) catalytic cycle is proposed (Scheme 3d). Following ligand enabled C—H cleavage, oxidative addition of H_2O_2 to Pd(II) forms the high valent Pd(IV) species which subsequently undergoes reductive elimination to form the hydroxylated product. Ligand exchange with 2HX forms water as the sole byproduct and regenerates the catalyst PdX_2.

3. Conclusion

In summary, we have developed a practical C(sp^2)—H hydroxylation of carboxylic acid substrates using hydrogen peroxide aqueous solution as the hydroxylating reagent, enabled by a newly developed bifunctional carboxyl-pyridone (CarboxPyridone) ligand. Mechanistic studies indicate that this ligand scaffold play a crucial role in achieving room temperature C—H activation, thus permitting the development of mild reaction conditions which preclude the decomposition of hydrogen peroxide. With this new protocol, a wide range of phenylacetic acids and benzoic acids were successfully hydroxylated, providing the corresponding phenols. The practicality and scalability of the reaction was highlighted by large scale examples including a 1000 mmol scale reaction of ibuprofen, suggesting the transformation may have the potential to be applied to industrial scale processes. Furthermore, the derivatizations of phenol products and synthesis of trifluorinated coumestan and pterocarpene were achieved.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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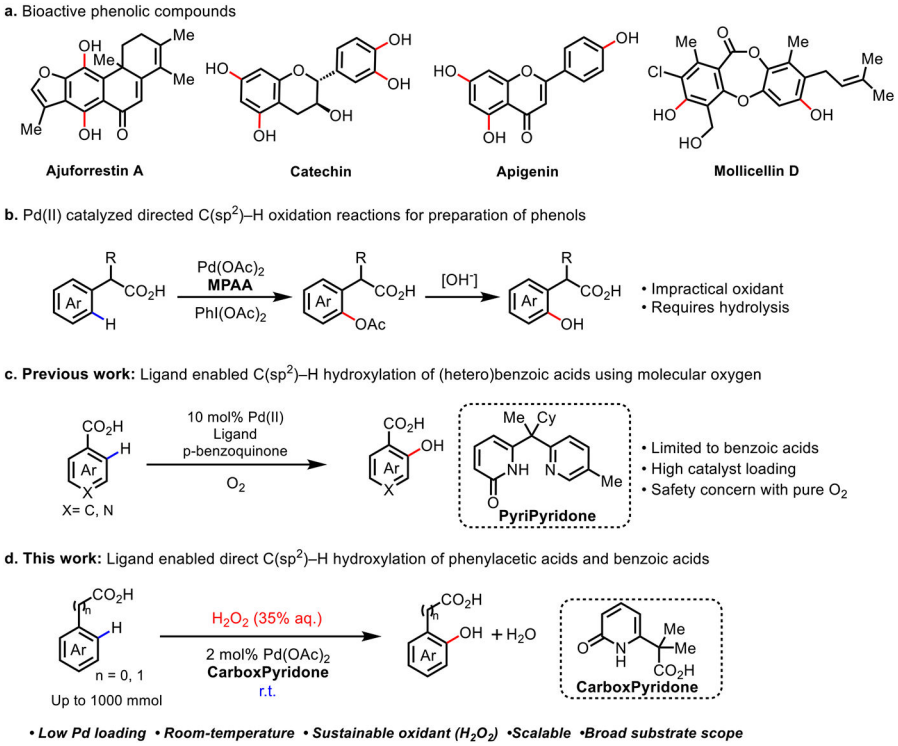
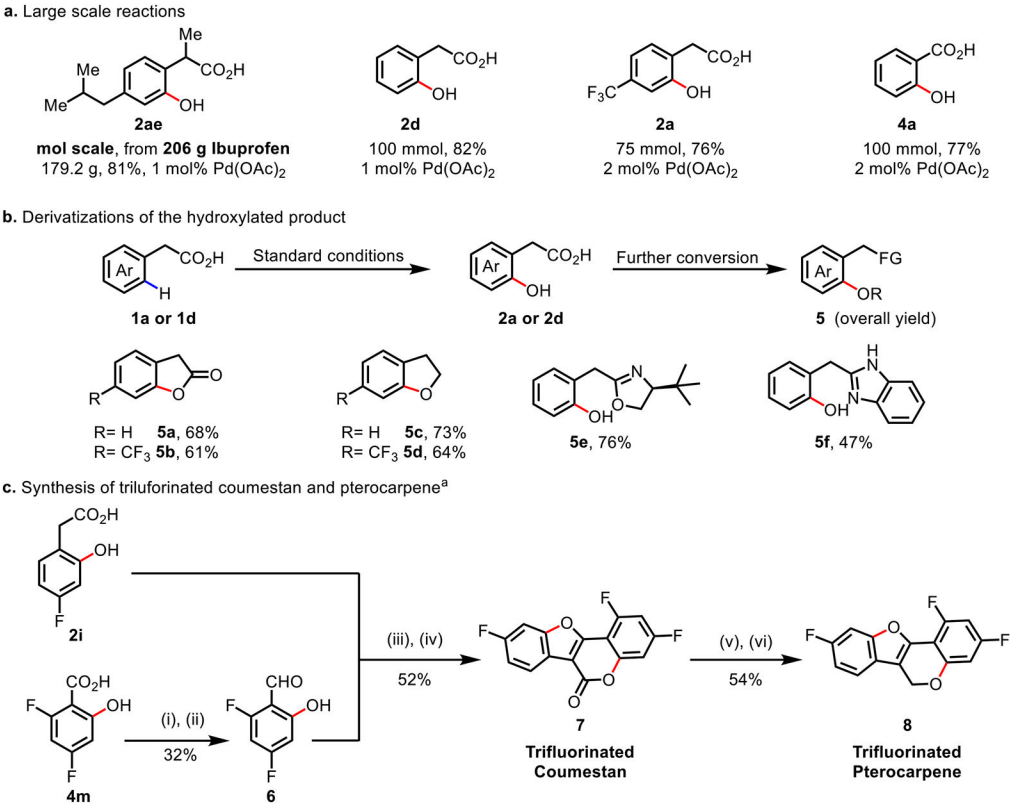


Scheme 1.

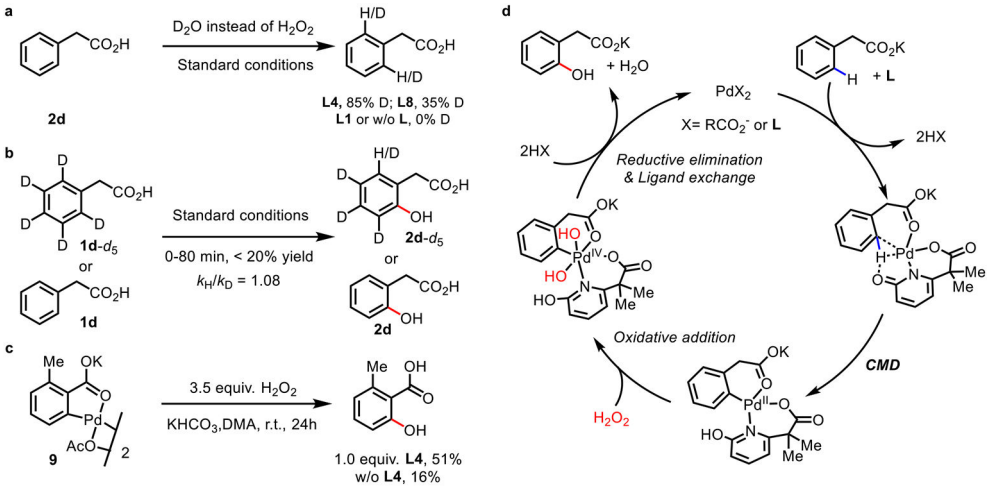
Preparation of Phenols through Pd(II) catalyzed C(sp^2)—H Oxidations



Scheme 2.

Synthetic Applications

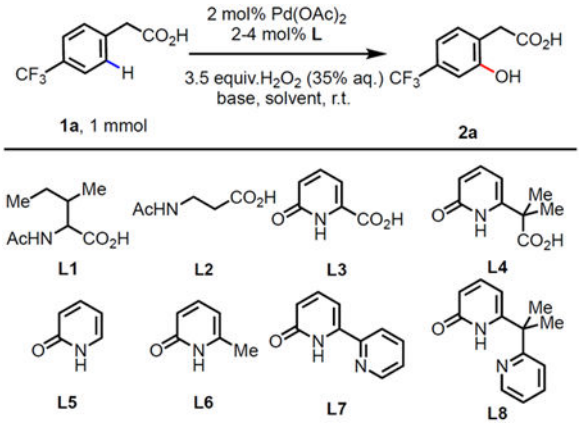
[a]Conditions: (i) $LiAlH_4$, THF, 50 °C. (ii) PCC, DCM, r.t.. (iii) Ac_2O, NaOAc, AcOH, 110 °C. (iv) DDQ, toluene, 120 °C. (v) $LiAlH_4$, THF, 50 °C. (vi) I_2, imidazole, PPh_3, CH_3CN/ Et_2O r.t.. (See supporting information for detailed procedures)



Scheme 3.
Mechanistic Studies and Proposed Catalytic Cycle

Table 1.

Optimization of the C(sp^2)—H Hydroxylation Using Hydrogen Peroxide[a]



Entry	Ligand	Base	Solvent	Yield (%)
1[b]	**L1**	K_2HPO_4	DMA	37
2	**L1**	K_2HPO_4	DMA	0
3	**L2**	K_2HPO_4	DMA	0
4	**L3**	K_2HPO_4	DMA	0
5	**L4**	K_2HPO_4	DMA	65
6	**L5**	K_2HPO_4	DMA	trace
7	**L6**	K_2HPO_4	DMA	trace
8[c]	**L7**	K_2HPO_4	DMA	<5
9[c]	**L8**	K_2HPO_4	DMA	0
10	**No L**	K_2HPO_4	DMA	0
11	**L4**	$KHCO_3$	DMA	80
12	**L4**	K_2HPO_4	CH_3CN	86

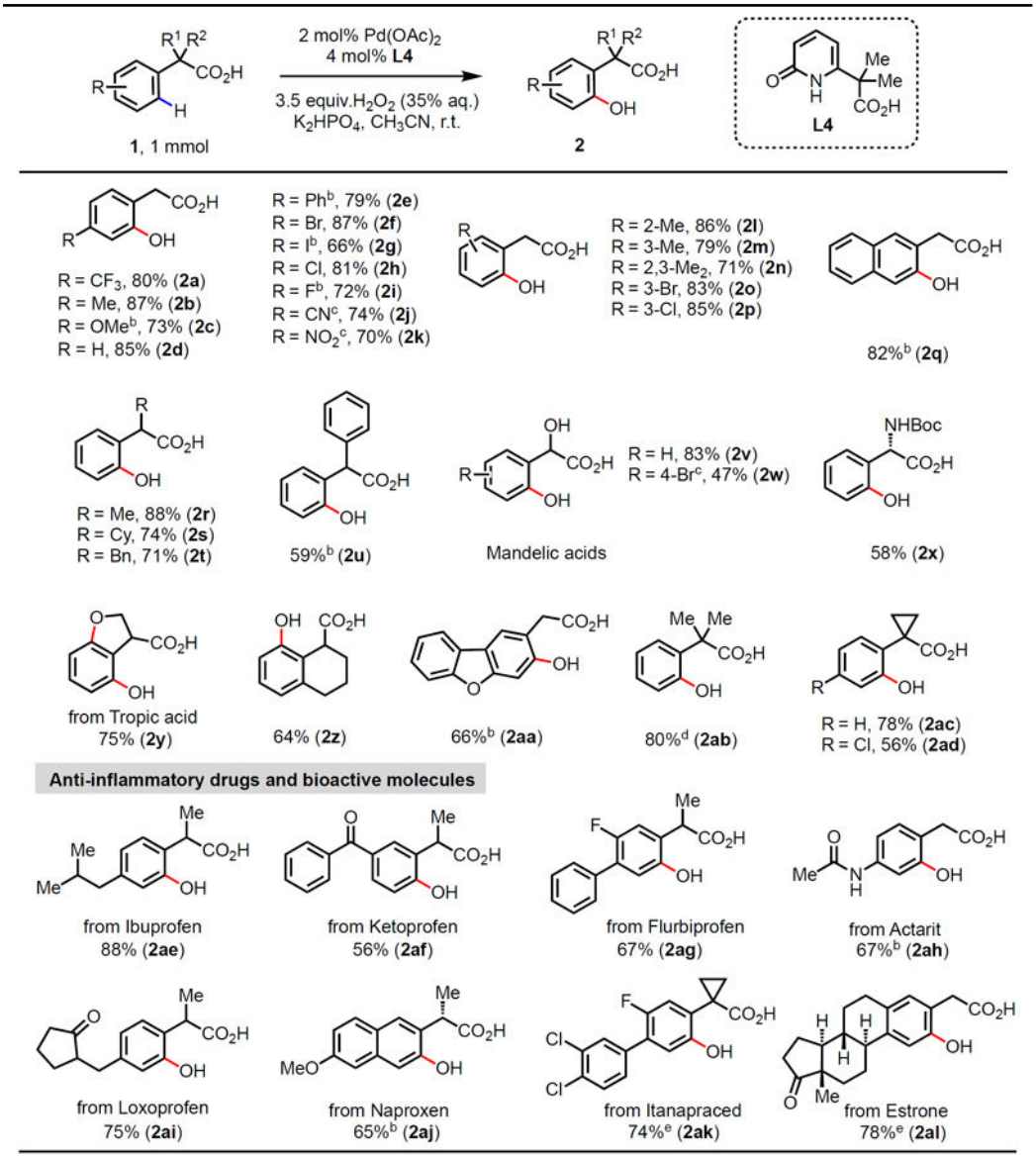
[a]Conditions: 4-Trifluoro-phenylacetic acid (1.0 mmol), $Pd(OAc)_2$ (2 mol%), ligand (4 mol%), H_2O_2 (35% aqueous solution, 3.5 equiv.), base (1.5 equiv.) in solvent (3.0 mL) r.t., 24 h. Yields were determined by ^1H NMR using CH_3NO_2 as the internal standard.

[b]90°C.

[c]2 mol% ligand.

Table 2.

Ligand enabled C(sp^2)—H hydroxylation of phenylacetic acids[a]



[a]Conditions: Carboxylic acid **1** (1 mmol), $Pd(OAc)_2$ (2 mol%), **L4** (4 mol%), H_2O_2 (35% aqueous solution, 3.5 equiv.), and K_2HPO_4 (1.5 equiv.) in CH_3CN (3.0 mL), r.t., 24 h. Isolated yields.

[b]$KHCO_3$ (2 mmol) instead of K_2HPO_4, DMA instead of CH_3CN.

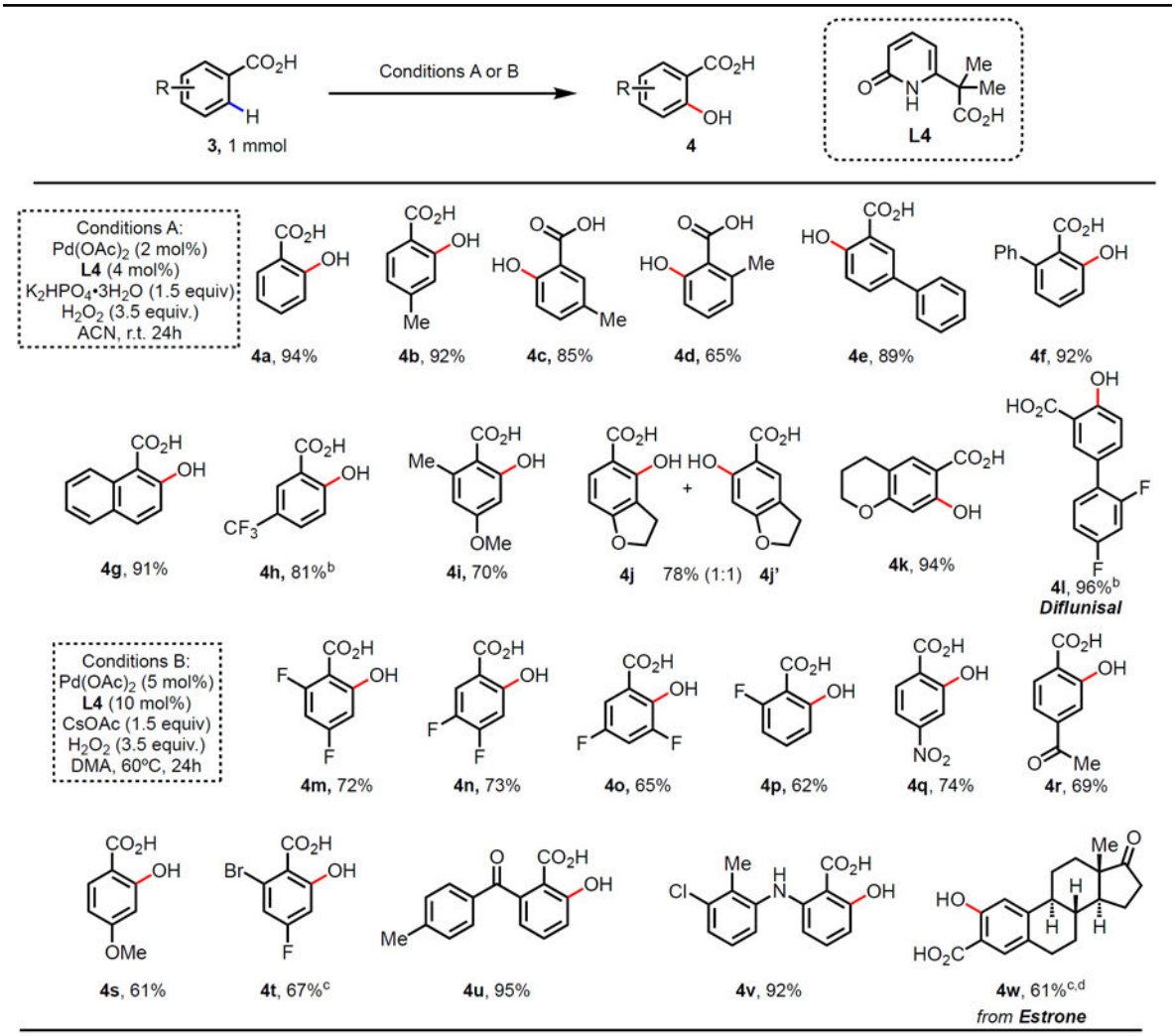
[c]60 °C.

[d]Isolated yield based on the corresponding lactone. (See SI for details)

[e]0.5 mmol scale.

Table 3.

Ligand enabled C(sp^2)—H hydroxylation of benzoic acids[a]



[a]Conditions **A**: Carboxylic acid **3** (1 mmol), $Pd(OAc)_2$ (2 mol%), **L4** (4 mol%), H_2O_2 (35% aqueous solution, 3.5 equiv.), and K_2HPO_4•$3H_2O$ (1.5 equiv.) in CH_3CN (3.0 mL), r.t. 24 h.; Conditions **B**: Carboxylic acid **3** (1 mmol), $Pd(OAc)_2$ (5 mol%), **14** (10 mol%), H_2O_2 (35% aqueous solution, 3.5 equiv.), and CsOAc (1.5 equiv.) in DMA (3.0 mL), 60 °C. 24 h. Isolated yields.

[b]60 °C

[c]K_2HPO_4•$3H_2O$ instead of CsOAc, 48h.

[d]0.5 mmol scale, r.t.