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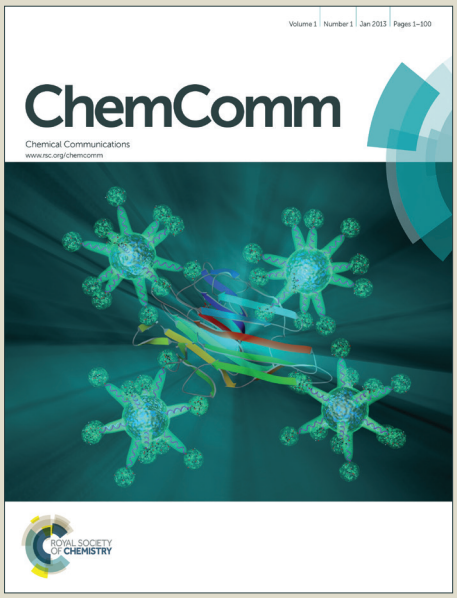

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DOI: 10.1039/C5CC04952K

Journal Name

COMMUNICATION

Unactivated C(sp^3)-H Hydroxylation through Palladium Catalysis with H_2O as the Oxygen Source

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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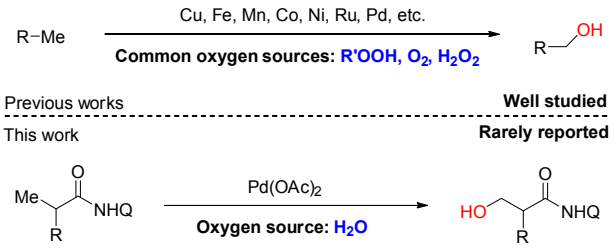
A novel palladium catalyzed hydroxylation of unactivated aliphatic C(sp^3)-H bonds was successfully developed. Different from conventional methods, water serves as the hydroxyl group source in the reaction. This new reaction demonstrates good reactivity and broad functional group tolerance. The C-H hydroxylated products can be readily transformed into various highly valuable chemicals via known transformations. Based on experimental and theoretical studies, a mechanism involving Pd(II)/(IV) pathway is proposed for this hydroxylation reaction.

Introduction

In the past decade, transition-metal-catalyzed direct functionalization of C–H bonds has gradually emerged as valuable and practical tools for organic synthesis.[1] Among these studies, C-H oxygenation[2] reactions which introduce a hydroxyl functional group into molecules have received much attention owing to its broad application in pharmaceutical and material industry. In general, the hydroxyl group can be introduced from three potential sources: 1) *in situ* hydrolysis of newly installed acyloxyl groups,[3] such as OAc, OTFA, OBz, etc.; 2) peroxides[4], molecular oxygen[5] or ozone[5] (Scheme 1); 3) molecular water[6]. Compared with the other two common sources, the use of environmentally benign water as the hydroxyl source is particularly attractive because of the advantages of high atom economy, low cost and high safety. However, in contrast to the other two major approaches, much less progress has been made in this area. Up to date, there are only few reported examples[7] to involve water as the hydroxyl source, including well-known Wacker oxidation[8], which involves water as a nucleophile to construct C(sp^2)-O bonds with ethylene. Although the employment of water as the hydroxyl source may possess great advantages, transition-metal catalyzed reactions conducted in aqueous solution are often confronted with great challenges owing to the potential 'poisonous' effect of molecular water to transition-metal and the heterogeneity of reaction mixture. Furthermore, molecular water generally is a relatively poor nucleophile in organic reactions.

Inspired by the seminal C(sp^3)-H acetoxylation work by Corey[9] and recent advances by Pd(II)/(IV) catalysis with a bidentate directing group[10], we envisioned that Pd(II)/(IV) may provide a viable solution for the C(sp^3)-H hydroxylation with water. Compared to Pd(II)/(0) pathway, Pd(II)/(IV) would be more electrophilic and less sensitive to water. In addition, Pd(II)/(IV) cycle would result in less potential catalyst precipitation than Pd(II)/(0) catalysis. Our aim was to identify suitable Pd(II) catalyzed C(sp^3)-H hydroxylation conditions with water via Pd(II)/(IV) cycle for the preparation of valuable aliphatic alcohols (Scheme 1). Herein, we report the first example of hydroxylation of unactivated C(sp^3)-H bonds with H_2O through palladium catalysis.



Scheme 1 Hydroxylation of unactivated C(sp^3)-H bonds by metal catalysis.

To test our hypothesis, 8-aminoquinoline (AQ) protected 2-methylbutyric acid **1** was chosen for the model study (Table 1). At the beginning of our investigations, a variety of oxidants, such as $PhI(OAc)_2$, 1,4-benzoquinone (BQ), Selectfluor, $K_2S_2O_8$, $Na_2S_2O_8$, oxone, $NaIO_4$, and Dess-Martin Periodinane (DMP), etc, were examined in the presence of $Pd(OAc)_2$ in alcohol/water cosolvent system. After many fruitless attempts, to our delight, the desired βC-H

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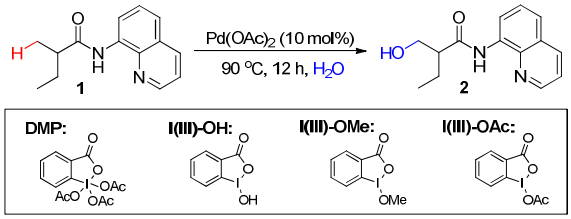
hydroxylation compound **2** was observed in a NMR yield of 35% along with 60% of unreacted **1** after stirring for 12 hours at 90 °C with $Pd(OAc)_2$ and DMP[11], in the cosolvent of *i*-PrOH/water (1:1) (entry 1). Meanwhile, a trace amount of alkoxylated product could be observed by LC-MS analysis. Considering DMP (I^{5+}) can react with alcohols to *in-situ* generate the cyclic hypervalent iodine (I^{3+}) reagent, we proposed cyclic I^{3+} reagent might be the true oxidant of this hydroxylation reaction. Therefore, three readily available cyclic I^{3+} reagents[12] (for details, seeSupporting Information) were tried. As expected, these three oxidants gave improved yields of roughly 50% accompanied with 2-iodobenzoic acid as the byproduct (entries 2-4). Encouraged by this initial findings, we started to optimize the reaction conditions by screening various organic solvents mixed with H_2O (v:v/1:1). *t*-BuOH, THF, dioxane, nitromethane and acetone were found to give the desired product with similar or improved yields and acetone gave the best result with 55% yield (entry 6). Further investigations indicated that product **2** could be obtained in an isolated yield of 64% along with 20% of unreacted **1** at 100 °C (entry 8). Among various Pd(II) catalysts tested, $Pd(OAc)_2$ proved to give the best yield (see Supporting Information). Control experiments confirmed the necessity of palladium catalyst, oxidant and water for this reaction (entry 9).

Table 1 Optimization of the reaction conditions

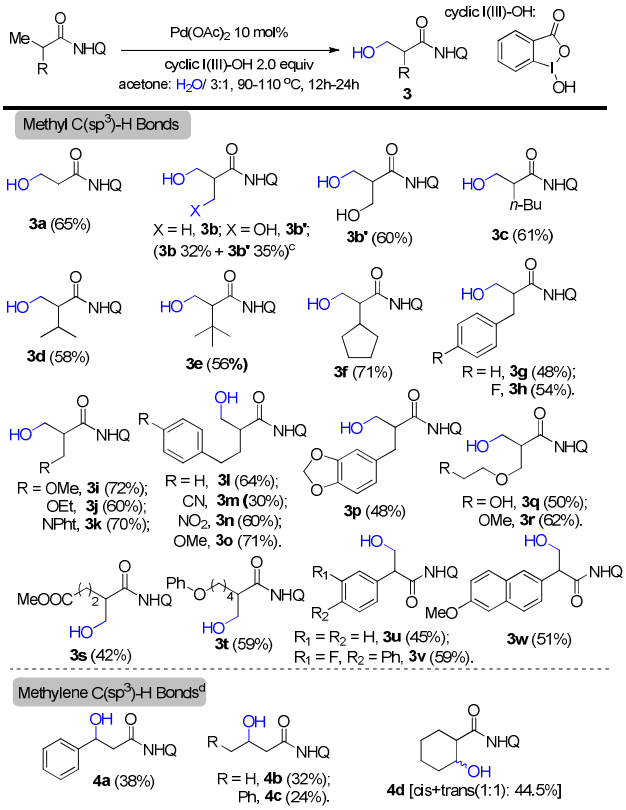


Entry	Conditions	Yield (%)[a]
1	DMP 2.0 equiv, *i*-PrOH/H_2O (1:1)	35
2	I(III)-OH 2.0 equiv, *t*-BuOH/H_2O (1:1)	48
3	I(III)-OMe 2.0 equiv, *t*-BuOH/H_2O (1:1)	48
4	I(III)-OAc 2.0 equiv, *t*-BuOH/H_2O (1:1)	48
5	I(III)-OH 2.0 equiv, THF/H_2O (1:1)	38
6	I(III)-OH 2.0 equiv, acetone/H_2O (1:1)	55
7	I(III)-OH 2.0 equiv, acetone/H_2O (3:1)	65
8	I(III)-OH 2.0 equiv, acetone/H_2O (3:1), 100°C	70 (64)[b]
9	without $Pd(OAc)_2$, oxidants or water	0

[a] NMR Yields using 4-nitrobenzaldehyde as the internal standard; [b] Isolated yield;

With the optimized conditions in hand, we began to explore the substrate scope and limitations of this AQ-directed C(sp^3)-H hydroxylation reactions. The scope of this new C-H hydroxylation reaction was found to be broad. As illustrated in Table 2, various alkyl (methyl, *n*-butyl, isopropyl, *tert*-butyl, cyclopentyl, benzyl, etc) (**3a-3t**) at the alpha position were compatible to the reaction conditions and most of them afforded desired product in moderate to good yields (50%-72%). In these cases, hydroxylation reactions on secondary or tertiary C-H bonds were rarely observed. Differently substituted aryl groups, as well as the electron-rich (**3o, 3p**) and electron-deficient (**3m, 3n**) aryl groups, were also tolerated. Substrates with heteroatoms in the beta position could be smoothly transformed into corresponding alcohols (**3i-3k**). Gratifyingly, our method could be successfully used to modify two representative pharmaceutical drugs[13] to afford novel hydroxylated analogues (**3v-3w**), which were difficult to be obtained by conventional methods. Phenomenon accompanied with the moderate to good isolated yields in most cases is partially remaining of the starting materials with little decomposition. Additionally, more challenging substrates with sterically hindered methylene C(sp^3)-H bonds were tested and gave relatively low yields of hydroxylated products along with greater than 50% recovered starting materials (**4a-4d**). It is noteworthy to point out that installing a hydroxyl group on molecules can serve two general and important purposes: 1) the hydroxyl group can be further converted into various functional groups; 2) the water solubility of targeted molecules can be greatly improved.

Table 2 Substrate scope[a,b]



[a] standard reaction conditions for C-H hydroxylation on a 0.10-0.30mmol reaction scale for 12-24h; [b] isolated yield; [c] cyclic I(III)-OH 3.0equiv; [d] $Pd(OAc)_2$ 20 mol%.

To demonstrate practicality of this synthetic methodology, large-scale reactions were conducted to give corresponding hydroxylated product **3l** and **3v** in satisfactory yields with partially recovered starting materials ([Eq. (1) and (2)]). As illustrated in Scheme 2, the hydroxylated products can be

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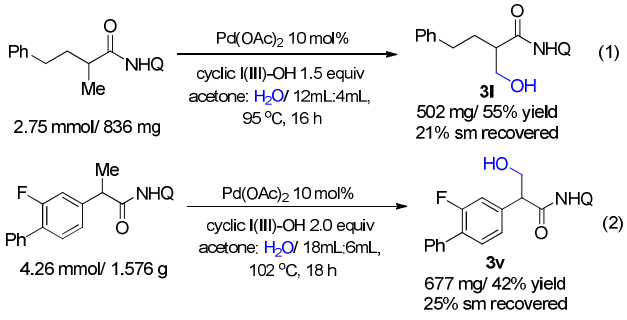
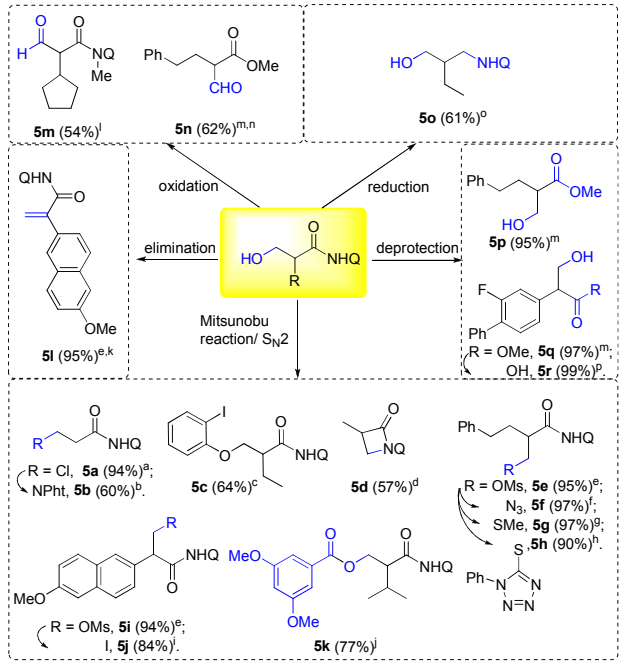
readily converted to various valuable derivatives through known chemical transformations. For instance, aldehydes **5m**, **5n** were obtained by oxidation and 3-amino alcohol **5o** was prepared via reduction with $LiAlH_4$. α,β-Unsaturated amide **5l** can be accessed in a yield of 95% via elimination. The acidic deprotection can cleave the directing group and afford corresponding alcohols **5p** and **5q** in good yields. Additional hydrolysis of **5q** would furnish α,β-hydroxyl acid **5r**. Mitsunobu reaction with varied nucleophiles can further transform the hydroxyl group into different functional groups in satisfactory yields, such as aliphatic halides (**5a**, **5j**), β-amino acid **5b**, aryl ether **5c**, thio ethers (**5g**, **5h**), β-lactam **5d**, aliphatic azide **5f**, and aryl ester **5k**, etc.

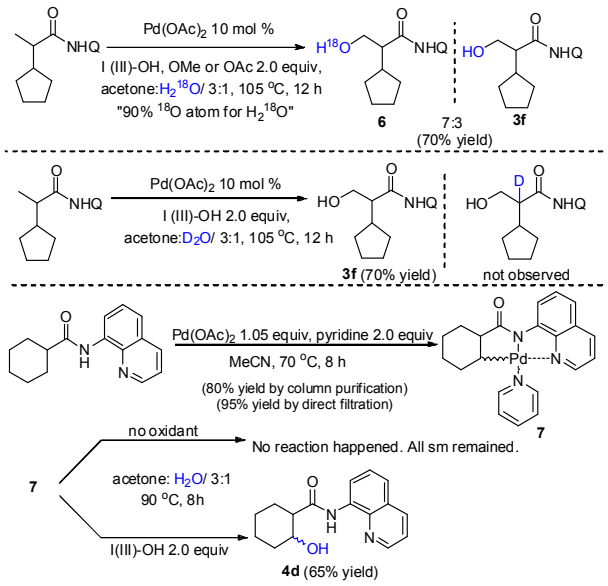




Conditions: a) $SOCl_2$, DCM, reflux, 12h; b) PPh_3, DIAD, Phthalimide, THF, 0°C-rt, 1h; c) MsCl, Et_3N, DCM, 0°C, 1h; 2-iodophenol, $Cu(OAc)_2$, K_2CO_3, DMF, 70°C, 2h; d) MsCl, Et_3N, DCM, 0°C, 1h; NaSMe, DMF, 50°C, 1.5h; e) MsCl, Et_3N, DCM, 0°C, 1h; f) NaN_3, $Cu(OAc)_2$, DMF, 70°C, 2h; g) NaSMe, $MeOH/H_2O$, rt, 2h; h) 1-phenyl-1H-tetrazole-5-thiol, K_2CO_3, DMF, 70°C, 2h; i) NaI, acetone, reflux, 48h; j) PPh_3, DIAD, 3,5-dimethoxybenzoic acid, THF, 0°C-rt, 1h; k) K_2CO_3, acetone, reflux, 48h; l) TBDBSCl, imidazole, THF, rt, 1h; *t*-BuOK, MeI, THF, rt, 2h; TBAF, THF, rt, 4h; DMP, DCM, rt, 1h; m) conc.H_2SO_4, MeOH, 105°C, 12h; n) DMP, rt, 1h; o) $LiAlH_4$, THF, 0 °C-rt, 6h; p) LiOH, $MeOH/H_2O$, rt, 1h.

Scheme 2 Product transformations.

Further studies were performed to gain insights into the reaction mechanism. One possible reaction pathway would involve β-H elimination, which was followed by oxa-Michael addition to provide the desired product. As depicted in Scheme 3, to test this possibility, deuterated water and acetone were used as the cosolvent in the reactions. However, compound **3f** was formed in a good yield of 70% and none of the corresponding α-deuterated compound was found, which should exclude the above-proposed mechanism. The use of $H_2{}^{18}O$ instead of $H_2{}^{16}O$ generated compound **6** as the major product, which was confirmed by LC-MS and NMR analysis (for details, see Supporting Information). These results clearly showed that the oxygen atom in the hydroxyl group originated from water. Next, the cyclic palladated complex **7** was prepared and used in the following reactions. The experimental results showed that no desired product was observed without cyclic I^{3+} oxidant, otherwise roughly 65% of hydroxylated product **4d** was obtained. Therefore, it was suggested that Pd(II) needed to be oxidized to Pd(IV)[14] before affording the C-H hydroxylation product.



Scheme 3 Mechanistic studies.

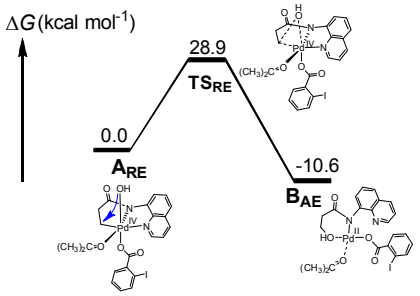


Fig. 1 DFT-calculated reaction profile of intramolecular reductive elimination (RE) mechanism for the final C-O bond formation of

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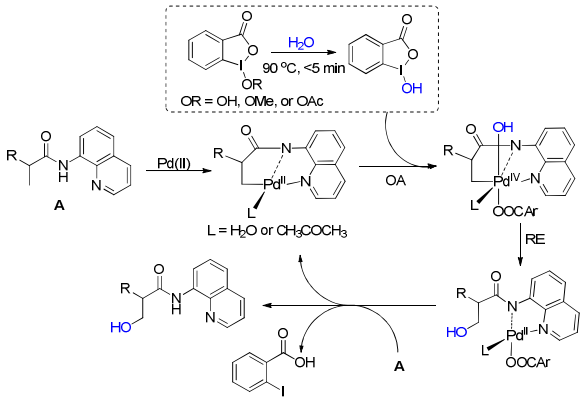
hydroxylation.

After formation of Pd(IV) species, as to the key final C-O bond formation step, we explored the intramolecular reductive elimination (RE) process to give the hydroxylated product and regenerate Pd(II) by using DFT theoretical calculation. As shown in Figure 1. We can see that via a transition state $\mathbf{TS_{RE}}$, RE needs to overcome a reaction barrier of 28.9 kcal mol^{-1}, which implies that RE mechanism for the final C-O bond formation is a feasible one in the current reaction system.



Scheme 4 Plausible mechanism.

Although some details of the mechanism remain to be ascertained, based on our experimental and computational studies, a plausible mechanism was proposed (Scheme 4). The first step involves AQ-directed C(sp^3)-H activation by $Pd(OAc)_2$ to form a bicyclic five-membered cyclopalladated intermediate, which was then oxidized by ligand exchanged cyclic I^{3+} reagent to generate Pd(IV) complex. Reductive elimination afforded Pd(II) coordinated hydroxylated product, which reacts with another substrate to afford final product and restart the catalytic cycle.

In summary, we have developed the first Pd(II)-catalyzed hydroxylation of C(sp^3)-H bonds with water as a unique hydroxyl group source. The prepared hydroxylated products are highly valuable building blocks for further chemical transformations and this new hydroxylation reaction can also be employed to modify drugs efficiently. This new reaction demonstrates good reactivity and broad functional group tolerance. Further studies on the application and mechanism of this new reaction are in progress in our laboratory.

Acknowledgements

This work was supported by the national '973' grant from the Ministry of Science and Technology (grant # 2011CB965300), National Natural Science Foundation of China (grant # 21302106, 21290194, 21221002, 21473215) and Tsinghua University Initiative Scientific Research Program.

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