Catalytic Hydroxylation

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Pd-Catalyzed C–H Oxygenation with TFA/TFAA: Expedient Access to Oxygen-Containing Heterocycles and Late-Stage Drug Modification**

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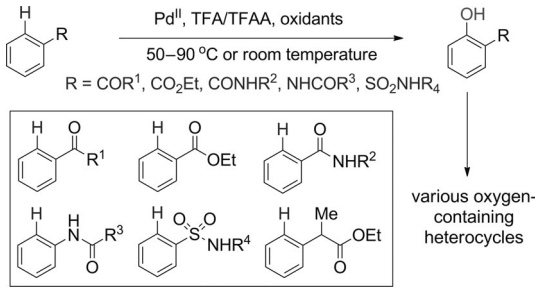
Dedicated to Professor Geert-Jan Boons on the occasion of his 50th birthday

Functionalized phenols are valuable industrial chemicals related to pharmaceuticals, agrochemicals, and polymers.[1] Therefore, the direct catalytic hydroxylation of arenes to produce phenols has attracted much attention. Although tremendous progress has been made in this field, there are still difficult substrates which remain unmet challenges for direct hydroxylation in terms of regio- and chemoselectivity, as well as the practicality of current methods (Scheme 1). For



Scheme 1. A new general approach to functionalized phenols.

example, 2-hydroxy aromatic ketones are useful synthetic intermediates for the preparation of various oxygen-containing heterocycles such as benzofuranone, chromanone, benzoxazole, and dibenzooxazepine; they also serve as key building blocks for drugs such as celiprolol, acebutolol, and propafenone. Traditional strategies for accessing 2-hydroxy aromatic ketones have mainly involved the oxidation of benzylic alcohols,[2] the hydrolysis of aromatic halides,[3] Fries rearrangement of esters[4] or the demethylation of methyl phenyl ether.[5] These methods generally suffer from one limitation or another, such as tedious reaction procedures, harsh reaction conditions, low yields, or the formation of side products. Hence, direct transformation of readily available aromatic ketones into valuable 2-hydroxylated products by transition metal-catalyzed C–H functionalization is arguably a highly efficient and atom-economic method to access these compounds. Moreover, developing a more general strategy for the regio- and chemoselective C–H oxygenation of a variety of challenging arenes would be especially desirable for phenol synthesis (Scheme 1).

In the last decade, C–H bond activation catalyzed by the weak coordination of transition metals,[6,7] especially palladium,[8] for the synthesis of aromatic and heteroaromatic compounds has proven to be highly selective and atom economical. In our continuous studies of preparing functionalized phenols, we envisioned that palladium(II) catalysts, under the proper acidic conditions, could allow C–H bond cleavage by an *ortho*-metalation process through weak coordination with the carbonyl oxygen of aryl ketones, benzoates, benzamides, or even the sulfonyl oxygen of sulfonamides.[9,10] Consequently, in theory, a C–O bond formation is possible by reductive elimination to afford the corresponding phenols with suitable acids[11] (Scheme 1). To the best of our knowledge, the direct catalytic *ortho*-hydroxylation of aryl ketones, benzoates, benzamides, acetanilides, and sulfamides with a mixture of trifluoroacetic acid and trifluoroacetic anhydride (TFA/TFAA) and palladium(II) has not yet been achieved. Herein, we report the first example of Pd^{II}-catalyzed regioselective C–H oxygenation of these substrates and its convenient application to the synthesis of oxygen-containing heterocycles and late-stage drug modification. Of particular note, it was found that the reaction can actually be effectively performed at room temperature. Our preliminary mechanistic study discovered the dual role of TFA/TFAA as both the oxygen source and the essential factor for C–H activation.

To test our hypothesis, we initiated a model study with aromatic ketone **1** in the presence of $Pd(OAc)_2$ in AcOH/Ac_2O solvent system with $PhI(OAc)_2$ as the terminal oxidant (Ac = acetyl; Table 1). However, neither acetoxylated nor hydroxylated products were formed. After many unsuccessful attempts, we turned our attention to more acidic systems, such as TCA/TCAA (TCA = trichloroacetic acid) and TFA/TFAA. To our delight, the phenol product **2** was observed in less than 10% yield with TCA/TCAA (entry 2) and 32% yield with TFA/TFAA after stirring for 10 h at 100 °C (entry 3). This initial result suggests that Pd^{II} catalyzed C–H activation, with the carbonyl oxygen of aryl ketones as an

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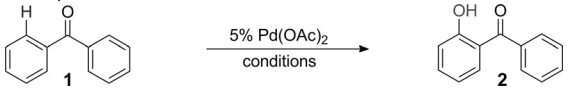
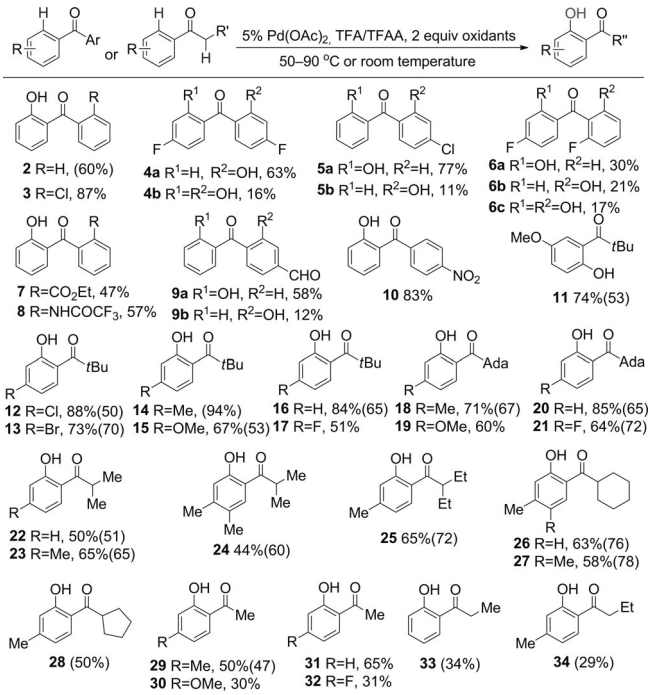
Table 1: Optimization of the reaction conditions.



Entry	Oxidant[a]	Conditions[b]	Yield[c] [%]
1	$PhI(OAc)_2$	pyridine, AcOH/Ac_2O, 100 °C, 10 h	NR
2	$PhI(OAc)_2$	TCA/TCAA, 100 °C, 10 h	< 10
3	$PhI(OAc)_2$	TFA/TFAA, 100 °C, 10 h	32
4	$Cu(OAc)_2$	TFA/TFAA, 100 °C, 10 h	NR
5	BQ	TFA/TFAA, 100 °C, 10 h	NR
6	oxone	TFA/TFAA, 100 °C, 10 h	trace
7	benzoyl peroxide	TFA/TFAA, 100 °C, 10 h	9
8	*tert*-butyl peroxide	TFA/TFAA, 100 °C, 10 h	NR
9	NFSI	TFA/TFAA, 100 °C, 10 h	56
10	selectfluor	TFA/TFAA, 100 °C, 3 h	61 (77)[d]
11	selectfluor	TFA/TFAA, 100 °C, 3.5 h	80
12	selectfluor	pyridine, TFA/TFAA, 100 °C, 4 h	77
13	$PhI(OAc)_2$	TFA/TFAA, 100 °C, 4 h	60
14	$PhI(CF3CO_2)_2$	TFA/TFAA, 100 °C, 4 h	32
15	$K_2S_2O_8$	pyridine, TFA/TFAA, 100 °C, 4 h	76
16	$K_2S_2O_8$	TFA/TFAA, 100 °C, 4 h	75
17	$K_2S_2O_8$	TFA/TFAA, 100 °C, 3 h	76
18	$K_2S_2O_8$	$[PdCl_2(MeCN)_2]$, TFA/TFAA, 100 °C, 2 h	46
19	$K_2S_2O_8$	$[PdCl_2(PPh_3)_2]$, TFA/TFAA, 100 °C, 2 h	40
20	$K_2S_2O_8$	$Pd(CO_2CF_3)_2$, TFA/TFAA, 100 °C, 2 h	61
21	$K_2S_2O_8$	$[Pd(acac)_2]$, TFA/TFAA, 100 °C, 2 h	46

[a] 1.1 equiv of oxidant were used. [b] In all cases a 9:1 ratio of acid to anhydride was used. [c] Yield of isolated product. [d] Conversion is shown in parentheses. Ac = acetyl, acac = acetylacetonate, BQ = 1,4-benzoquinone, NSFI = *N*-fluorobenzenesulfonimide, NR = no reaction, TCA = trichloroacetic acid, TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride.

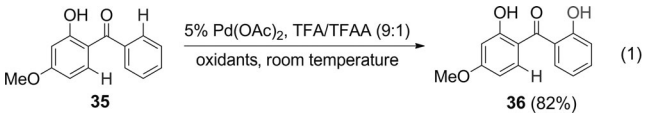


Scheme 2. Regio- and chemoselective hydroxylation of aryl ketones. Reactions conducted at room temperature. Yields shown are of isolated products. Data in parentheses are yields from reactions conducted at room temperature.

effective coordinating group, could happen under certain acidic conditions. Apparently, the strong acidity of TFA played a key role in this reaction. Encouraged by these preliminary results, we began to optimize the reaction conditions. After extensive testing, we found that selectfluor[12] and $K_2S_2O_8$[13] were superior to other oxidants. It was found that a high ratio of TFAA will significantly slow down the speed of the reaction and that a ratio of TFA/TFAA of around 9:1 is most suitable for the reaction. There are only slight differences with the addition of ligands such as pyridine in terms of reaction rates and conversion ratios. Some other Pd^{II} catalysts were tested in the reaction as well, such as $[PdCl_2(MeCN)_2]$, $[PdCl_2(PPh_3)_2]$, $Pd(CF_3CO_2)_2$, and $[Pd(acac)_2]$ (acac = acetylacetonate), but were not as efficient as $Pd(OAc)_2$. Generally, 0.05 equiv of $Pd(OAc)_2$ was enough to effectively promote the reaction. It was also noted that the reaction time can actually be shortened, the reaction typically proceeds to completion within 3–4 h at 90 °C.

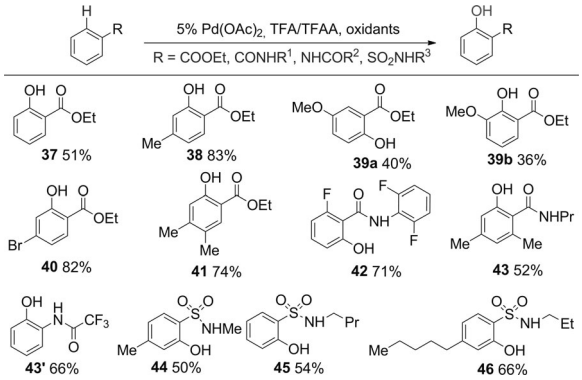
With these optimized conditions in hand, we next set out to explore the scope of this new reaction. As displayed in Scheme 2, a variety of aromatic ketones were smoothly transformed into the corresponding phenol products in moderate to excellent yields. The scope of the substituents was found to be very broad. Aryl groups with *ortho*, *meta*, and *para* substituents, as well as electron withdrawing and electron donating functional groups (such as halides, esters, amides, aldehydes, alkyl, nitro, and methoxy groups) were well tolerated. For unsymmetrical diaryl ketone substrates, the more electron-rich parts were preferentially hydroxylated (**5**, **9**, **10**). In some cases, dihydroxylated products (**4b**, **6c**) were also obtained in minor amounts. To our delight, when ketones containing easily oxidizable α-protons were tested, it was found that these ketones can also be transformed into hydroxylated products (**22**–**34**) with remarkable chemoselectivity. These phenols are either difficult to prepare or require tedious additional steps with traditional methods. During our investigation, it was noticed that many substrates can be facilely transformed into products at 50–60 °C in a short period of time (3–4 h), which caused us to wonder if the reactions could be run at room temperature. Surprisingly, our test results showed that aryl ketone substrates can be converted into the desired phenol products at ambient temperature (Scheme 2), albeit over a longer reaction time (typically 24–48 hrs). To the best of our knowledge, this is the only example of a phenol synthesis by Pd-catalyzed C–H activation that has been accomplished at room temperature. Some substrates, such as ketones containing reactive α-protons (**24**–**27**), produced better yields at room temperature than at higher temperature. More intriguingly, dioxybenzone (**36**), an organic compound widely used in sunscreen to block UVB and short-wave UVA rays,[14] was readily prepared by our new method at room temperature without the need to protect the free hydroxy group of **35**, which supports both the practicality and effectiveness of this novel

approach. Moreover, this reaction was conducted without the need for air-and water-free conditions [Eq. (1)].



(1)

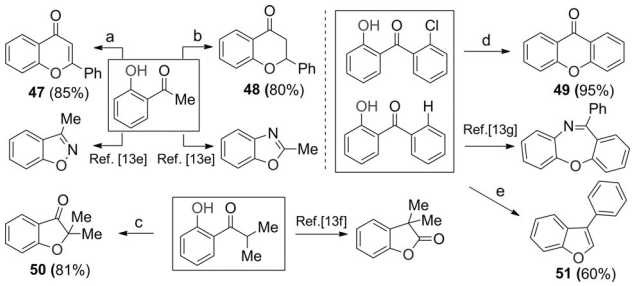
Subsequently, the reaction conditions were applied to other substrates, including benzoates, benzamides, acetanilides, and sulfonamides. As displayed in Scheme 3, we were very pleased to find that these three types of compounds were successfully transformed into the corresponding phenol products in modest to good yields. For sulfonamides in particular, this is the first time that these compounds have been directly converted into *ortho*-hydroxylated sulfonamides, which can serve as valuable synthetic intermediates for quick access to analogues of the billion-dollar drug tamsulosin.[15]



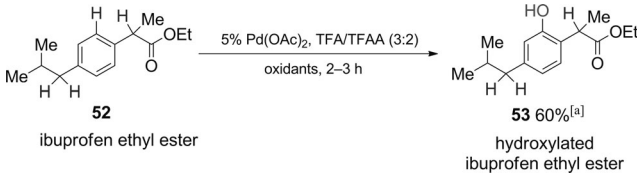
Scheme 3. Benzoate, benzamide, acetanilide, and sulfonamide as substrates. Yields shown are of isolated products. Pr = propyl.

To demonstrate the synthetic utility of this C–H oxygenation reaction, a variety of biologically important oxygen-containing heterocyclic compounds were prepared from 2-hydroxylated aryl ketone products. As shown in Scheme 4, chromanone **48**, benzofuran-3(2*H*)-one **50**, and benzoxazole derivatives, as well as more challenging heterocycles such as xanthone **49** and dibenzooxazepine can be readily accessed from the corresponding 2-hydroxylated ketones using known transformations.[16]

Late-stage modification of drug candidates by C–H activation is a particularly attractive approach for modern drug discovery, which greatly depends on the practicality of such chemical processes. Therefore, in Scheme 5 we show the feasibility of our new reaction by performing direct regio- and chemoselective C–H oxygenation of ibuprofen ethyl ester **52** (a representative nonsteroidal anti-inflammatory drug), which can provide a new approach to prepare novel ibuprofen analogues. As aromatic ketones, esters, amides, and sulfonamides are common scaffolds in drugs and natural products, this method can potentially open a facile route to rapid access of hydroxylated analogues of a broad range of substrates.

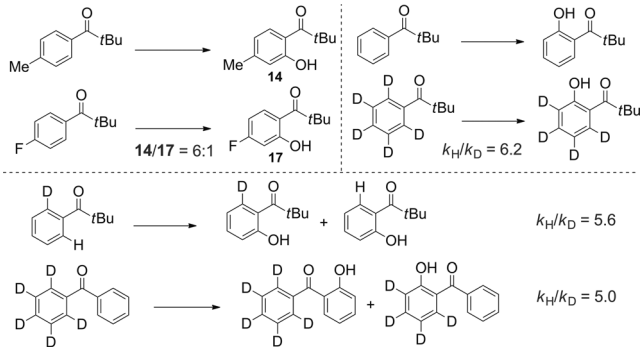


Scheme 4. Transformations of 2-hydroxy aromatic ketones into various oxygen-containing heterocycles. Conditions: a) benzaldehyde, NaOH, EtOH, RT, 12 h, 72%; I_2, DMSO, reflux, 1 h, 85%. b) Benzaldehyde, NaOH, EtOH, RT, 12 h, 72%; AcOH, reflux, 144 h, 80%. c) Tf_2O, pyridine, CH_2Cl_2, −78 °C–RT, 2 h, 83%; DBU, DMF, 0.2 h, 81%; d) KOH, H_2O, 100 °C, 15 h, 95%; e) CuOAc, K_2CO_3, 8-hydroxyquinoline, O_2, DMA, 140 °C, 24 h, 60%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMA = dimethylacetamide, DMF = dimethylformamide, DMSO = dimethylsulfoxide, Tf = trifluoromethanesulfonyl.



Scheme 5. Regio- and chemoselective modification of ibuprofen. [a] % conversion.

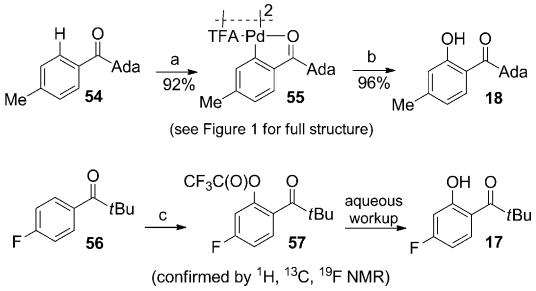
Further investigations were performed to gain some insight into the reaction mechanism, which is shown in Scheme 6. The result of parallel competition experiments surely shows that the electron-rich aromatic ring reacts much faster than its electron-poor counterpart (**14**/**17** 6:1). Furthermore, consistent and significant KIE values were observed from both intra- ($k_H/k_D = 5.6$) and intermolecular ($k_H/k_D = 5.0$ and 6.2) isotope effect studies, which indicated that the C–H bond cleavage step might be involved in the rate-limiting step of this transformation.



Scheme 6. Separate rate constants and KIE studies. Conditions for all reactions shown: Pd^{II}, TFA/TFAA, $K_2S_2O_8$.

To elucidate the effect of TFA/TFAA in this oxygenation reaction and to clarify the oxygen source, we conducted

a series of experiments designed to investigate the mechanistic pathway (Scheme 7). This included the preparation of a crystal of reaction intermediate **55** (Figure 1) with a stoichiometric amount of $Pd(OAc)_2$, which underwent a subse-



Scheme 7. Investigation of the mechanistic pathway. Conditions: a) 100% $Pd(OAc)_2$, TFA, RT. b) $K_2S_2O_8$, RT, TFA/TFAA. c) 5% $Pd(OAc)_2$, $K_2S_2O_8$, TFA/TFAA, RT. Ada = adamantyl.

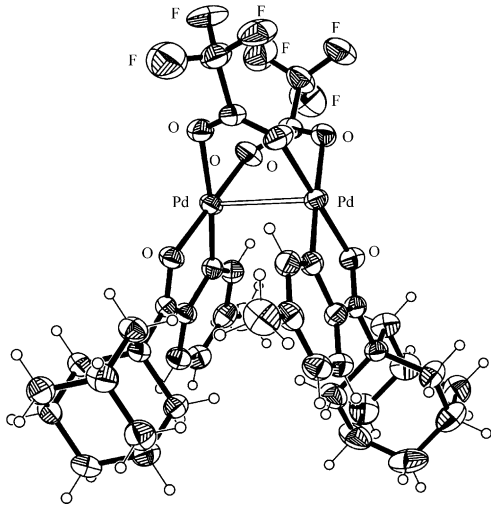
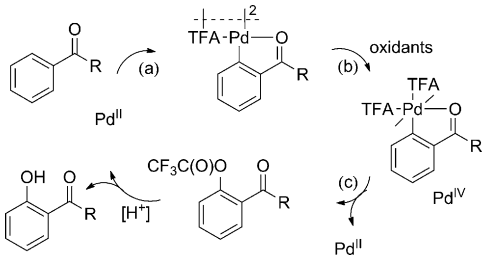


Figure 1. Crystal structure of **55**. Ellipsoids set at 35% probability.

quent oxidation with $K_2S_2O_8$ to afford the desired product **18**. The trifluoroacetate-substituted product **57** (confirmed by NMR analysis) was also obtained from the reaction, which, upon aqueous workup and purification by silica gel column chromatography was completely converted into the phenol product **17**. These results clearly supported the double effects of TFA/TFAA as: 1) being the essential factor for C–H activation and 2) serving as the oxygen source. Although TFA is normally viewed as a harsh chemical which should be avoided, based on our observation, we propose that TFA/TFAA could actually be employed as a useful and practical reagent for Pd-catalyzed direct C–H oxygenation of arenes in phenol synthesis.[17]

Although details about the mechanism remain to be ascertained, on the basis of our studies a plausible mechanism for this reaction is shown in Scheme 8. Step a involves the chelation of palladium to the carbonyl oxygen atom of the ketone substrate. The following chelate-directed C–H activation of the substrate could afford a five-membered cyclo-



Scheme 8. Proposed mechanism.

palladium(II) dimeric intermediate. In step b, Pd^{II} is oxidized into a possible Pd^{IV} intermediate.[18] The final step, step c, involves carbon–oxygen bond-forming reductive elimination to afford the trifluoroacetated product and to turn Pd^{IV} back into Pd^{II}. The trifluoroacetated product is then converted into a hydroxylated ketone after aqueous workup.

In summary, a novel Pd^{II} catalyzed regioselective phenol synthesis has been developed for the production of a broad range of functionalized phenols from easily accessible materials, such as aryl ketones, benzoates, benzamides, acetanilides, and sulfonamides. It was found that C–H oxygenation can even be carried out at room temperature. Preliminary mechanistic studies reveal that the TFA/TFAA solvent system serves as both the critical C–H functionalization factor and as the oxygen source. The reaction demonstrates excellent reactivity, *ortho*-selectivity, good functional group tolerance, and high yields. Its utility has been well exemplified in further synthetic applications and the late-stage modification of drugs. By employing a combination of Pd^{II} catalysts, oxidants, and TFA/TFAA, we have discovered a highly effective catalyst system for this unique regioselective oxygenation reaction. Further studies into the scope and the mechanism of this reaction are in progress in our laboratory.

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