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A General Approach towards Catechol and Pyrogallol through Ruthenium- and Palladium-Catalyzed C–H Hydroxylation by Weak Coordination

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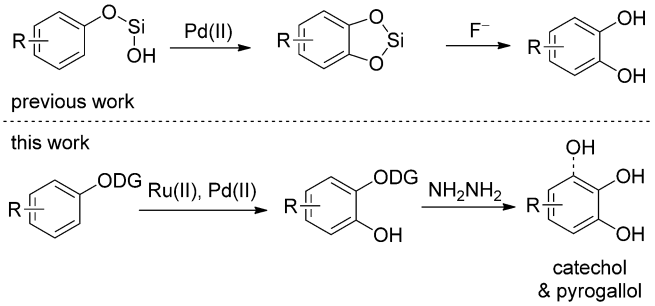
Abstract: An efficient ruthenium(II)- and palladium(II)-catalyzed C–H hydroxylation of aryl carbamates has been developed for the facile synthesis of catechols and pyrogallols. The reaction demonstrates excellent reactivity, regio- and chemoselectivity, good functional group compatibility and high yields. The practicality of this method has been proved by a gram-scale synthesis.

Keywords: catechol; C–H hydroxylation; palladium; ruthenium; weak coordination

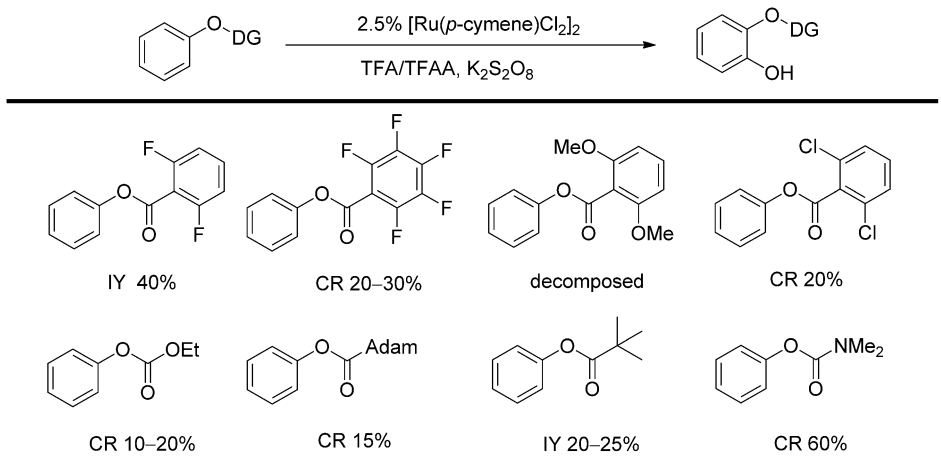
Catechols are common structural motifs found in many natural products and drugs.[1] Classic approaches[2] to the synthesis of catechols generally involve (i) an *ortho*-formylation of phenols followed by a subsequent Dakin oxidation or (ii) the oxidation of phenols into *ortho*-quinones followed by a reduction. However, these reactions lack site selectivity and always provide a mixture of *ortho*-, *meta*- and *para*-isomers. In 2009, Que and Akimova disclosed an iron-promoted hydroxylation of benzoic ac ids with H_2O_2.[3a] In the same year, Yu's group discovered a novel Pd(II)-catalyzed hydroxylation of benzoic acids with O_2 or air as the oxidant under non-acidic conditions.[8i] More recently, Gevorgyan and co-workers reported an elegant Pd-catalyzed silanol-directed *ortho*-C–H oxygenation which features high site selectivity and a broad functional group tolerance.[3b,c] In 2013, Martin group developed a formal copper-catalyzed C–H hydroxylation assisted by benzoic acids.[3d] In our continuous studies of developing new general tools for functionalized phenol synthesis, we are particularly interested in the development of an alternative C–O bond formation[4,5] as an interesting and useful addition to current protocols for catechol synthesis.

Recently, our group have reported examples of Ru(II)-, Rh(II)- and Pd(II)-catalyzed *ortho*-hydroxylation of benzoates, benzamides and aryl ketones in the trfluoroacetic acid/trifluoroacetic anhydride (TFA/TFAA) system.[6] Accordingly, based on our experience and understanding of this chemistry, we envisaged that ruthenium[7] and palladium[8] catalysts, under certain acidic conditions, could promote C–H bond activation *via* an *ortho*-metalation process through weak coordination with the carbonyl oxygen of phenol carbamates,[9] carbonates or esters. Following that step, a potential subsequent C–O bond formation *via* a reductive elimination could afford the corresponding catechol derivatives with suitable acids and oxidants[10] (Scheme 1). Herein, we report a novel catechol and pyrogallol synthesis through Ru(II)- and Pd(II)-catalyzed regio- and chemoselective C–H hydroxylation reaction.[11,12]

To test our hypothesis, different protected phenol esters, carbonates and carbamates were explored under previously reported conditions (Scheme 2). Delightfully, most substrates can be transformed into the corresponding desired products, albeit in relatively



Scheme 1. Developing a new approach for catechols by Ru, Pd catalysis.

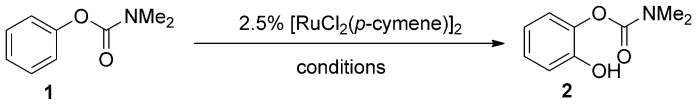


Scheme 2. Investigating directing groups.

low yields. Among them, phenyl dimethylcarbamate gave the best yield. Encouraged by promising preliminary results, next, we started an optimization of the reaction conditions with phenol carbamate **1**. A variety of oxidants was examined in the reaction, such as $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, $PhI(OAc)_2$ and Selectfluor (Table 1). Among them, $(NH_4)_2S_2O_8$ and $PhI(OAc)_2$ have similar and moderate capacities, but were less efficient than $K_2S_2O_8$. It was found that a ratio of TFA/TFAA of around 1:1 is most suitable for the reaction. Except for the desired products, no double-hydroxylation products were observed in all cases. Interestingly, it was noticed that the reaction can be carried out at room temperature (entry 13), although at a much slower rate. It was apparent that the transformation cannot happen in the absence of the ruthenium catalyst (entry 14). It was observed that the reaction is rather fast and typically will proceed to completion within 2–3 h at 70–90 °C.

With the optimal conditions in hand, we next began to survey the reaction scope. As showed in Table 2, a variety of phenol carbamates was efficiently transformed into the desired catechol derivatives in good to excellent yields. In comparison to $Pd(OAc)_2$, the

Table 1. Optimization of the reaction conditions.

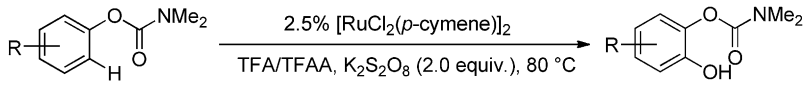


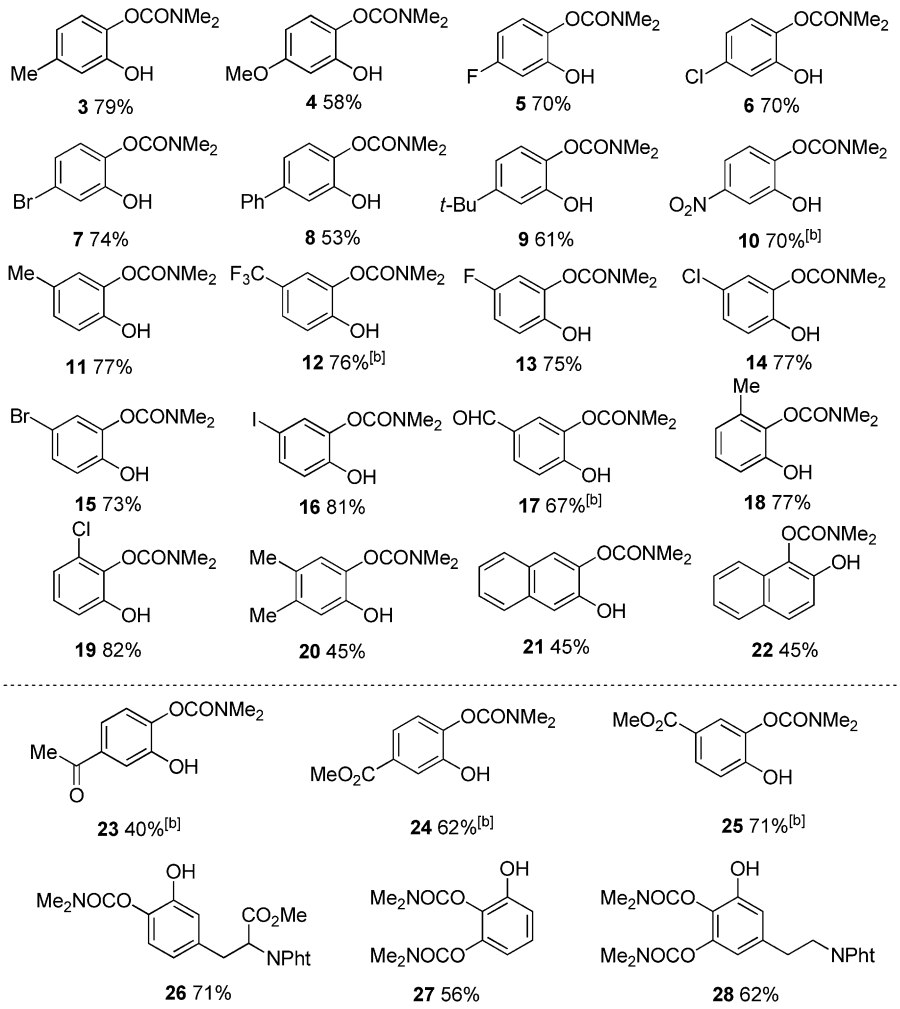
1 2

Entry	Oxidants[c]	Conditions	Yield[a] [%]
1	$K_2S_2O_8$	TFA/TFAA = 3:1, 80 °C, 3 h	60
2	$PhI(TFA)_2$	DCE, 80 °C, 3 h	24
3	$Na_2S_2O_8$	TFA/TFAA = 3:1, 80 °C, 3.5 h	0
4	$(NH_4)_2S_2O_8$	TFA/TFAA = 3:1, 80 °C, 1.5 h	30
5	$PhI(OAc)_2$	TFA/TFAA = 3:1, 80 °C, 1.5 h	29
6	Selectfluor	TFA/TFAA = 3:1, 80 °C, 1.5 h	0
7	$K_2S_2O_8$	TFA, 80 °C, 2 h	41
8	$K_2S_2O_8$	TFA/TFAA = 9:1, 80 °C, 2 h	35
9	$K_2S_2O_8$	TFA/TFAA = 3:1, 80 °C, 2 h	69
10	$K_2S_2O_8$	TFA/TFAA =1:1 (10 equiv.), DCE, 80 °C, 2 h	0
11	$K_2S_2O_8$	TFA/TFAA = 1:1 (10 equiv.), TfOH (1.0 equiv.), DCE, 80 °C, 3 h	10
12	$K_2S_2O_8$	TFA/TFAA = 1:1, 80 °C, 2 h	78 (72[b])
13	$K_2S_2O_8$	TFA/TFAA = 1:1, r.t., 24 h	26
14[d]	$K_2S_2O_8$	TFA/TFAA = 3:1, 80 °C, 1.5 h	0

[a] Conversion ratio.
[b] Isolated yield.
[c] 2.0 equiv.
[d] No metal.

Table 2. Reaction scope.

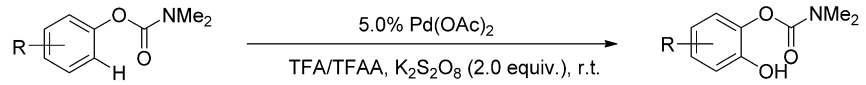


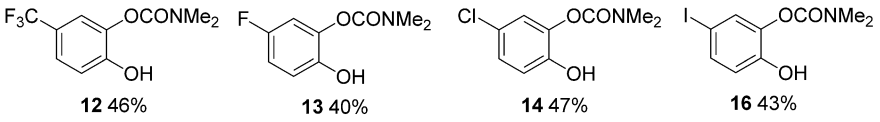


[a] Isolated yields.
[b] $PhI(OAc)_2$ (1.5 equiv.) as oxidant instead of $K_2S_2O_8$.

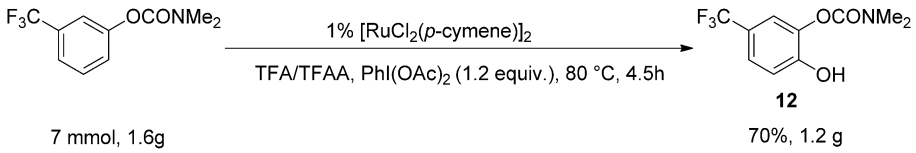
overall catalytic activity of $[RuCl_2(p\text{-cymene})]_2$ is better in terms of efficiency and both catalysts share similar selectivity. The scope of the substituents was found to be very broad. The *ortho*-, *meta*-, and *para*-substituted carbamates, as well as those with electron-withdrawing and electron-donating functional groups (methoxy, methyl, halides, CF_3, ester, nitro etc.) were well tolerated. For example, carbamates containing strong electron-withdrawing groups, such as NO_2 and CF_3 (**10**, **12**) could be smoothly transformed to the *ortho*-hydroxylated products in satisfactory yields. Impressively, the aldehyde and acetyl functional groups (**17**, **23**) were also compatible in this reaction, which demonstrated both the excellent regio- and chemoselectvity of this reaction. All *meta*-substituted carbamates gave only one regioisomeric product (**11**–**16**), due to steric hindrance. Interestingly, when several carbamates containing two different potential directing groups were examined in this reaction system, the carbamate group was superior over the ester and ketone groups in terms of directing ability (**23**–**25**). This new method provides new route for the construction of some biologically important molecules. For instance, L-DOPA (a biological active molecule in our body and a psychoactive drug used in the clinical treatment of Parkinson's disease and dopamine-responsive dystonia) can be easily accessed from catechol derivative **26** which was synthesized from protected L-tyrosine under the reaction conditions. Additionally, catechols can be further converted into syn-

Table 3. Room temperature reaction by palladium(II) catalysis.[a]

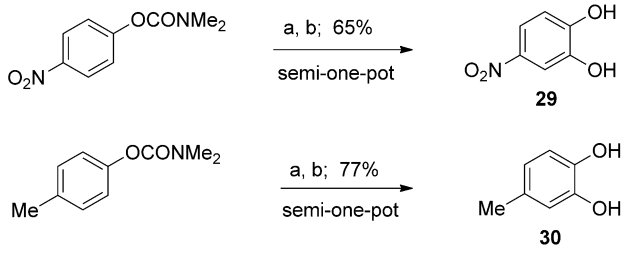




[a] Unoptimized yields.

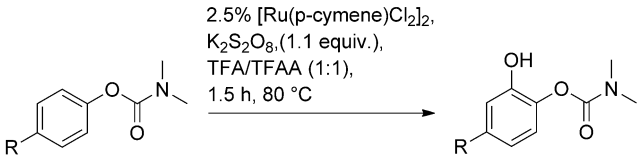


Scheme 3. Gram-scale synthesis.



conditions a) 2.5% $[RuCl_2(p\text{-cymene})]_2$, 1.5 equiv. $PhI(OAc)_2$ or 2.0 equiv. $K_2S_2O_8$, TFA/TFAA, 80 °C, 2.5–8 h.
conditions b) $NH_2NH_2{\cdot}H_2O$, r.t., 8 h.

Scheme 4. Semi-one-pot syntheisis of catechols.



R	NMR yield
H	36%
Ph	25%
F	25%
NO_2	15%

Scheme 5. Separate rate constants study.

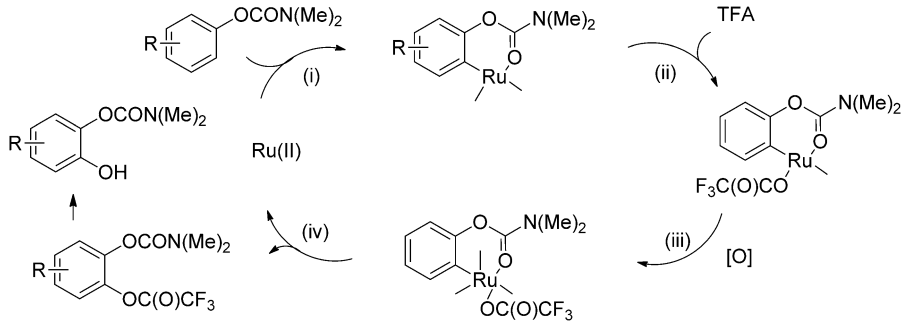
thetically challenging pyrogallols (**27**, **28**), which provides an alternative and efficient synthetic route to access valuable pyrogallol derivatives.

As displayed in Table 3, we are very pleased to find that actually phenol carbamates can be converted into the desired catechol products effectively by palladium catalysis at ambient temperature within a couple of hours, albeit in lower yields. Notably, this protocol was conducted without the need for air- or moisture-free reaction conditions.

To further prove practicality of this new approach, compound **12** was prepared on a gram scale (70% yield) under the optimized reaction conditions with only a 1 mol% $[RuCl_2(p\text{-cymene})]_2$ catalyst loading (Scheme 3). As shown in Scheme 4, the applicability and effectiveness of this reaction was further demonstrated in a sequential semi-one-pot hydroxylation/deprotection procedure which can directly transform carbamates to unprotected catechols (**29**, **30**) in good yields.

As shown in Scheme 5, parallel competition experiments have demonstrated that an electron-poor aromatic substrate reacted slower than its eletron-rich counterparts to give hydroxylated products. In addition, to probe the reaction mechanism, an intramolecular isotope effect study was conducted and only a small KIE value of 1.3 was observed (see the Supporting Information for more details). These results suggested that C–H activation may not be involved in the rate-limiting step of this transformation.

Although details about the mechanism remain unclear, a plausible mechanism (Scheme 6) for this reaction can be demonstrated as follows. Step (i) involves chelation of Pd(II)/Ru(II) to the carbonyl oxygen atom from the carbamate substrate and the following chelate-directed C–H activation of the substrate could afford a six-membered cyclometalate(II) intermediate. In the next steps (ii and iii), Pd(II)/Ru(II) was oxidized into a possible Pd(IV)/Ru(IV) intermediate. The final step (iv) involves carbon-oxygen bond-forming reductive elimination to afford the trifluoroacetylated product and turned Pd(IV)/Ru(IV)[13,14] back into Pd(II)/Ru(II). The trifluoroacetylated product was converted to catechol derivatives after an aqueous work-up.[6a]



Scheme 6. Plausible mechanism.

In summary, a unique Ru(II)- and Pd(II)-catalyzed regio- and chemoselective hydroxylation reaction has been developed for the synthesis of catechol and pyrogallol derivatives from easily accessible phenols. The reaction demonstrates excellent reactivity, *ortho*-selectivity, high yields and good functional group tolerance. The practicality of this new method was tested by a gram-scale synthesis. Further studies into the synthetic applications of this reaction are in progress in our laboratory.

Experimental Section

General Procedure I for Ruthenium- and Palladium-Catalyzed *ortho*-Hydroxylation of Carbamates

To a 15-mL sealed tube were added carbamate (1.0 equiv.), $K_2S_2O_8$ (2.0 equiv.) or $PhI(OAc)_2$ (1.5 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (0.025 equiv.) and TFA/TFAA(9:1–1:1). The tube was sealed and heated at 80 °C. The reaction was monitored by TLC (petroleum ether:ethyl acetate:triethylamine = 50:10:1). After completion of the reaction, H_2O (10 mL) was added and the reaction mixture was stirred for another half an hour. Then $NaHCO_3$ was added to neutralize TFA and TFAA and the mixture was extracted with DCM (3× 15 mL). Then the organic layer was dried over anhydrous Na_2SO_4 and concentrated on a rotavapor under reduced pressure. Finally, the residue was purified by silica gel column chromatography to give the desired products. When $Pd(OAc)_2$ was used as catalyst and $K_2S_2O_8$ as oxidant, the reaction could be carried out at room tempreture with moderate NMR yield.

General Procedure II for Catechol Synthesis

To a 15-mL sealed tube were added carbamate (1.0 equiv.), $K_2S_2O_8$ (2.0 equiv.) or $PhI(OAc)_2$ (1.5 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (0.025 equiv.), TFAA (1 mL) and TFA (1 mL). The tube was sealed and heated at 80 °C. The reaction was monitored by TLC (petroleum ether:ethyl acetate:triethylamine = 50:10:1). After completion of the reaction, the reaction mixture was diluted with dichloromethane and neutralized with saturated $NaHCO_3$, the organic layer was dried over anhydrous Na_2SO_4 and concentrated on a rotavapor under reduced pressure. Then 1 mL of $NH_2NH_2{\cdot}H_2O$ was added and the reaction mixture was stirred at room temperature for 8 h. Then H_2O was added and the resulting mixture was slowly acidified with concentrated HCl to pH = 1 and extracted with ethyl acetate, the organic layer was dried over anhydrous Na_2SO_4 and concentrated on a rotavapor under reduced pressure. Finally, the residue was purified by silica gel column chromatography to give the desired products.

Acknowledgements

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[13] For possible Pd(IV) intermediates in C–H functionalization reactions, see: a) T. Yoneyama, R. H. Crabtree, *J. Mol. Catal. A: Chem.* **1996**, *108*, 35; b) L. V. Desai, H. A. Malik, M. S. Sanford, *Org. Lett.* **2006**, *8*, 1141; c) K. M. Engle, T.-S. Mei, X. Wang, J.-Q. Yu, *Angew. Chem.* **2011**, *123*, 1514; *Angew. Chem. Int. Ed.* **2011**, *50*, 1478. For potential bimetallic Pd(III) species, see: d) D. C. Powers, M. A. L. Geibel, J. E. M. N. Klein, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 17050.

[14] Based on our investigations, it is possible that the rate-limiting step of this transformation may involve the oxidation step (the second step in the plausible mechanism), instead of the C–H activation step.

