PEER REVIEW FILE

Reviewers' comments:

Reviewer #1 (Remarks to the Author):

Selective oxidation is a key reaction in organic synthesis. In this manuscript, the authors developed an Ir-catelyzed tyrosinase-like approach to catechols via the formation of N-phenoxyacetamide intermediates, which are very useful building blocks for organic synthesis and pharmaceuticals. The experiment of the isotope labeling supported the plausible reaction mechanism. Moreover, this protocol provided an alternatively strategy to oxyacetamide-directed C–H hydroxylation on phenols and achieves one-pot synthesis of catechols with diverse substituent groups in good to excellent yield and high selective under mild conditions. Especially the example 2x, 2y, and 2z are very interesting and useful substrates. In my opinion, all the synthesis strategy represented the atom and step economical of direct C-H functionalization in orgainc chemistry, this report deserves to be published in the Nature Commun.

Reviewer #2 (Remarks to the Author):

The authors described the development of a new iridium-catalyzed tyrosinase-like approach to catechols, which used an oxyacetamide-directed C–H hydroxylation on phenols. This method can access catechols quickly via one-step, redox-neutral synthesis protocol and a variety of substituted catechol derivatives were prepared under mild conditions. Further mechanistic studies revealed that the directing group (DG) oxyacetamide served as the oxygen source in this reaction. The authors also prepared 18O-labeled catechols by using 18O-labeled acetic acid. The authors further demonstrated that this synthetic strategy can be applied to the synthesis of dopamine, L-dopa and estradiol from the corresponding phenols.

Overall, I think this is a quite interesting and useful work for providing a new protocol to synthesize catechols, which can be biologically prepared by ubiquitous tyrosinase catalyzes the aerobic oxidation of phenols to through the binuclear copper centers. I would like to recommend acceptance for publication in NC after addressing following questions.

Question 1:
The reaction scope need further investigations. For example, if heterocycle will be compatible in this reaction.

Question 2:
The authors should mention the easiness of starting materials.

Question 3:
If authors can do some computational study to reveal why Ir is capable is this re-dox reaction ? How about different Rh catalysts and if authors had extensively tried Rh catalysts ?

Question 4:
If authors can explain the role of acid additives, which seems to be a key thing for this new reaction.

Detailed Responses to Referee's Comments

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Response

We thank the reviewer for this nice comment.

Reviewer #2 (Remarks to the Author):

The authors described the development of a new iridium-catalyzed tyrosinase-like approach to catechols, which used an oxyacetamide-directed C–H hydroxylation on phenols. This method can access catechols quickly via one-step, redox-neutral synthesis protocol and a variety of substituted catechol derivatives were prepared under mild conditions. Further mechanistic studies revealed that the directing group (DG) oxyacetamide served as the oxygen source in this reaction. The authors also prepared 18O-labeled catechols by using 18O-labeled acetic acid. The authors further demonstrated that this synthetic strategy can be applied to the synthesis of dopamine, L-dopa and estradiol from the corresponding phenols.

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Question 1:
The reaction scope need further investigations. For example, if heterocycle will be compatible in this reaction.

Response

We thank the reviewer for this valuable advice. We made further investigations on one-step synthesis of complicated catechols with fluorescent property and bioactivity. Recently we reported a new method to afford different fluorescent heteroarylated

phenols by *N*-phenoxyacetamides. When *ortho*-heteroarylated *N*-phenoxyacetamide **1u** was subject to the standard *ortho*-hydroxylation conditions, the desired product 2-(2,3-dihydroxyphenyl)benzothiazole (2-DHPBT) derivative **2u** with green fluorescence was obtained in 76% yield. Our method could be a general strategy to prepare fluorescent dihydroxyl heterocycle scaffold. Next, we prepared the ONHAc-containing coumarins, the 7,8-dihydroxyl products **2v** and **2w**, with complete chemoselectivity in 87% and 81% yield respectively. The product 7,8-dithydroxycoumarin **2v** was commonly called Daphnetin and is an important natural product from Zushima with good anti-inflammatory and anti-oxidant activities. Our reaction could provide a powerful tool in the chemical synthesis of Daphnetin derivatives.

<u>Revisions Made</u>

(Please refer to page 3, paragraph 3, Table 3 and supporting information).

One-pot synthesis of different catechols with fluorescent property and bioactivity. Our method provided the possibility of one-step synthesis of complicated catechols (**Table 3**). Recently we reported a new method to afford different fluorescent heteroarylated phenols by *N*-phenoxyacetamides.[34] When *ortho*-heteroarylated *N*-phenoxyacetamide **1u** was subject to the standard *ortho*-hydroxylation conditions, the desired product 2-(2,3-dihydroxyphenyl) benzothiazole (2-DHPBT) derivative **2u** with green fluorescence was obtained in 76% yield. Our method could be a general strategy to prepare fluorescent dihydroxyl heterocycle scaffold.[48,49] Next, we prepared the ONHAc-containing coumarins, the 7,8-dihydroxyl products **2v** and **2w**, with complete chemoselectivity in 87% and 81% yield respectively. The product 7,8-dithydroxycoumarin **2v** was commonly called Daphnetin and is an important natural product from Zushima with good anti-inflammatory and anti-oxidant activities.[50,51] Our reaction could provide a powerful tool in the chemical synthesis of Daphnetin derivatives. Finally, bioactive catechols natural products such as L-dopa and estradiol were tested under the standard reaction conditions, the protected L-dopa **2x**, protected dopamine **2y** and estradiol **2z** were successfully obtained directly with high selectivity and excellent yields, highlighting the method's mild conditions ,excellent functional group tolerance, and selectivity.

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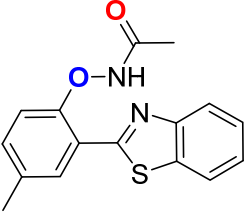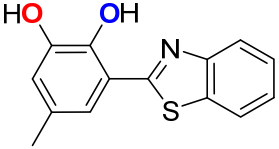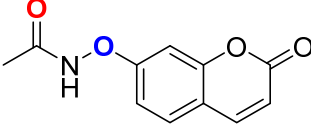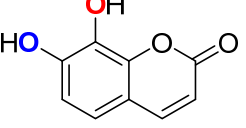49. Shindo, K., Shindo, Y., Hasegawa, T., Osawa, A., Kagami, O., Furukawa, K., & Misawa, N. Synthesis of highly hydroxylated aromatics by evolved biphenyl dioxygenase and subsequent dihydrodiol dehydrogenase. *Appl. Microbiol. Biot.* **75,** 1063-1069 (2007).
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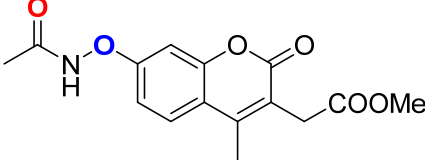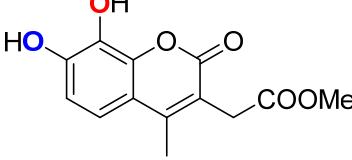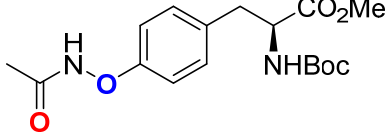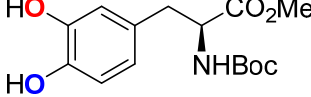
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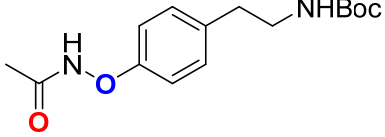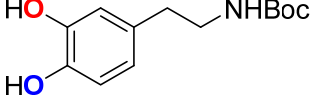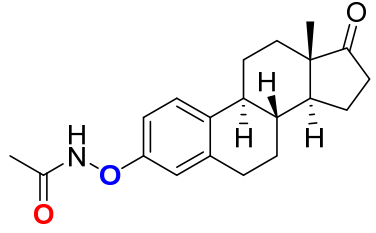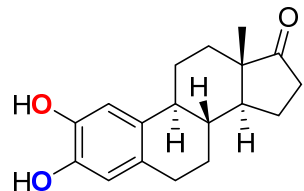51. Fylaktakidou, K. C., Hadjipavlou-Litina, D. J., Litinas, K. E., & Nicolaides, D. N. Natural and synthetic coumarin derivatives with anti-inflammatory/antioxidant activities. *Curr. Pharm. Design* **10,** 3813-3833(2004).

Table 3 | Scope of fluorescent and bioactive catechols

Entry	Substrate		Product		Yield[a,b]
1		1u	Fluorescent 2-DHPBT	2u	76%
2		1v	Daphentin	2v	87%
3		1w	Substituted Daphentin	2w	81%
4		1x	Protected L-dopa	2x	80%
5		1y	Protected Dopamine	2y	85%
6		1z	Estradiol	2z	72%

[a] Reaction conditions: 0.2 mmol **1**, 5 mol% [Cp*IrCl₂]₂, 2.5 equiv CH₂(COOH)₂ in 0.1 M MeOH at room temperature in air for 16 h. [b] Isolated yield.

Question 2:
The authors should mention the easiness of starting materials.

Response

We thank the reviewer for this kind suggestion. A variety of substituted substrates with O–NHAc directing group were easily prepared from phenols or aryl boronic acid compounds. Detailed synthesis procedures had been displayed in supporting information.

Revisions Made

(Please refer to page 2, paragraph 2 and supporting information Ⅱ).

A variety of substituted substrates with -O–NHAc directing group were easily prepared from phenols or aryl boronic acid compounds.[35-37, 41]

35. Endo, Y., Shudo, K., & Okamoto, T. An acid catalyzed rearrangement of *O*-aryl-*N*-benzoylhydroxylamines; synthesis of catechols from phenols. *Synthesis.* **6,** 461-463 (1980).
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Question 3:
If authors can do some computational study to reveal why Ir is capable is this re-dox reaction? How about different Rh catalysts and if authors had extensively tried Rh catalysts?

Response

We thank the reviewer for this helpful suggestion. Different kinds of catalysts had been screened and revealed in Supplementary Table 1. Rh catalyst with different valence state didn't work on this reaction. Regarding to the difference between Ir and Rh, we think that the size and redox behaviour of the two metals might contribute to the fine-tuning of their catalytic activity.

Revisions Made

The results were showed in revised manuscript.
(Please refer to page 2, paragraph 3 and supporting information Ⅲ).

We first explored Zn-, Al-, Fe-, Cu-, Pd- and Ru-catalyzed systems to *N*-phenoxyacetamides (**1a**). Unfortunately, the target product (**2a**) was not detected. The same result was shown in the common Rh-catalyzed system for -O–NHAc (**Table 1, entries 1–10** and **Supplementary Table 1**).

Table S1. The screen of reaction conditions.

Reaction scheme: 1a → 2a, Catalyst / Additive, Solvent / Oxygen source / T
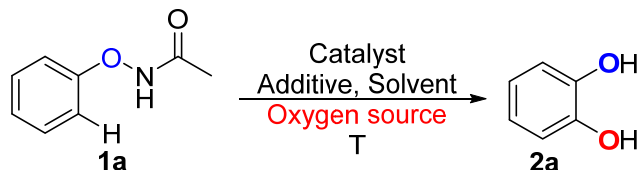
entry	catalyst[a]	additive	solvent	O source	T/°C	% yield[b]
1	[(COD)Rh(acac)]₂	2.5 eq. CH₂(COOH)₂	MeOH	—	r.t.	ND
2	[(COD)RhCl]₂	2.5 eq. CH₂(COOH)₂	MeOH	—	r.t.	ND
3	Rh(OAc)₂	2.5 eq. CH₂(COOH)₂	MeOH	—	r.t.	ND
4	[Cp*RhCl₂]₂	2.5 eq. CH₂(COOH)₂	MeOH	—	r.t.	ND
5	Pd(OAc)₂	2.5 eq. CH₂(COOH)₂	MeOH	—	r.t.	ND
6	Pb(acac)₂	2.5 eq. CH₂(COOH)₂	MeOH	—	r.t.	ND
7	Pb(PPh₃)₄	2.5 eq. CH₂(COOH)₂	MeOH	—	r.t.	ND
8	Pb(TFA)₂	2.5 eq. CH₂(COOH)₂	MeOH	—	r.t.	ND
9	[Cp*IrCl₂]₂	2.5 eq. HOOCCOOH	MeOH	—	r.t.	ND
10	[Cp*IrCl₂]₂	2.5 eq. TsOH	MeOH	—	r.t.	ND
11	[Cp*IrCl₂]₂	2.5 eq. CH₂CHCOOH	MeOH	—	r.t.	ND
12	[Cp*IrCl₂]₂	2.5 eq. TMBA	MeOH	—	r.t.	63
13	[Cp*IrCl₂]₂	2.5 eq. p-Toluic acid	MeOH	—	r.t.	46
14	[Cp*IrCl₂]₂	2.5 eq. 1-adamantoic acid	MeOH	—	r.t.	54
15	[Cp*IrCl₂]₂	2.5 eq. CH₂(COOH)₂	MeOH	—	r.t.	92
16	[Cp*IrCl₂]₂	2.5 eq. CH₂(COOH)₂	EtOH	—	r.t.	73
17	[Cp*IrCl₂]₂	2.5 eq. CH₂(COOH)₂	ⁱPrOH	—	r.t.	23
18	[Cp*IrCl₂]₂	2.5 eq. CH₂(COOH)₂	AmOH	—	r.t.	ND
19	[Cp*IrCl₂]₂	2.5 eq. CH₂(COOH)₂	Ethylene glycol	—	r.t.	15
20	[Cp*IrCl₂]₂	2.5 eq. CH₂(COOH)₂	MeCN	—	r.t.	ND
21	[Cp*IrCl₂]₂	2.5 eq. CH₂(COOH)₂	DMSO	—	r.t.	ND
22	[Cp*IrCl₂]₂	2.5 eq. CH₂(COOH)₂	THF	—	r.t.	ND

[a]

Reaction conditions: 0.2 mmol **1a**, 5 mol% catalyst, 5.0 mmol acid in 0.1 M solvent at room temperature under N_2 for 12 h. [b] GC yield.

Question 4:
If authors can explain the role of acid additives, which seems to be a key thing for this new reaction.

Response

We thank the reviewer for this helpful suggestion. Following this suggestion, we did two part computational study for evaluating the significance of acid additives. Theoretical calculations revealed that when acid additives were introduced, the free energy of species **A** underwent a significant reduction from 22.4 kcal/mol to 2.1 kcal/mol, highlighting the crucial role of acids in stabling species **A** and protonation. Further mass spectrometric experiments were carried out to explore the interaction between [Cp*IrCl₂]₂ and different acids (HCOOH, CH₂COOH and CH₂(COOH)₂). Interestingly, in the Ir/HCOOH/MeOH system, HCOOH was detected losing a molecule CO_2 fragment when interacted with [Cp*IrCl₂]₂ while CH₂COOH or CH₂(COOH)₂ dissociated one molecule CH₃COOH and CH₂(COOH)₂ respectively by collision induced dissociation (CID). This result might explain why HCOOH was ineffective in promoting the reaction.

Revisions Made

The acid might play several roles, such as preventing the generation of inactive intermediate **3**, consuming the by-product ammonia, and protonating the intermediate **C**. Further theoretical calculations revealed that when acid additives were introduced, the free energy of species **A** underwent a significant reduction from 22.4 kcal/mol to 2.1 kcal/mol, highlighting the crucial role of acids in stabling species **A** and protonation (**Supplementary Fig. S1**). Mass spectrometric experiments were carried out to explore the interaction between $[Cp*IrCl_2]_2$ and different acids (HCOOH, CH_2COOH and $CH_2(COOH)_2$) (**Supplementary Fig. S2**). Interestingly, in the Ir/HCOOH/MeOH system, HCOOH was detected losing a molecule CO_2 fragment when interacted with $[Cp*IrCl_2]_2$ while CH_2COOH or $CH_2(COOH)_2$ dissociated one molecule CH_3COOH and $CH_2(COOH)_2$ respectively by collision induced dissociation (CID). This result might explain why HCOOH was ineffective in promoting the reaction.

Supporting information:

V. Mechanism study
b) Theoretical calculations
Computational details:

All the calculations were performed with Gaussian 09 package.[5] Geometry optimization of all stationary points in gas phase was conducted by B3LYP method.[6] The LANL2DZ basis set[7] with ECP was used for Ir, and the 6-31G(d) basis set[8] was used for other atoms. Frequency analysis was performed for each optimized structure to verify the stationary points as either minima or saddle point at the same level of theory. Solvent effect (solvent=methanol) was included by single-point energy calculation using SMD[9] solvation model and B3LYP-D3 method[10] with the def2-TZVP basis set for Ir and 6-311++G(d, p) basis set for the other atoms.[11] All relative energies (corrected with zero point energy) and Gibbs free energies (at 298.15 K and 1 atm) are reported in kcalmol^{-1}.
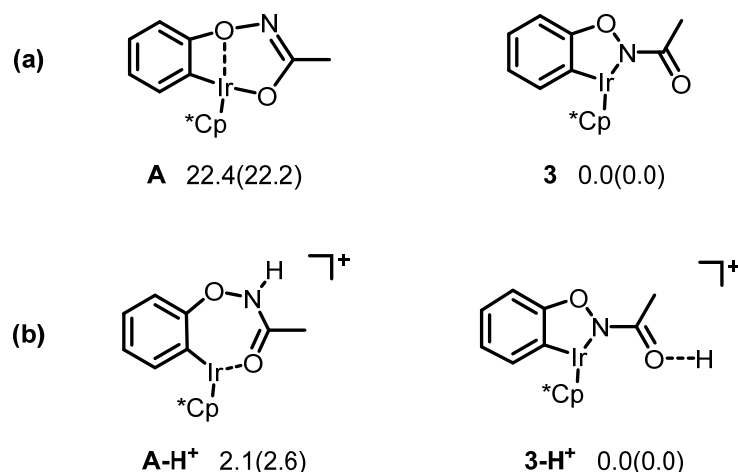

Figure S1 Intermediate **A** and intermediate **3** under netural state (**a**) and protonated state (**b**). Relative free energy and electronic energy (in parentheses) in solution are given in kcal/mol.

For netural mode, the free energy of species **A** is about 22.4 kcal/mol much higher than that of intermediate **3**, which indicates that in netural or basic condition intermediate **3** is favored.

While by introducing acid additives, species **A** could be stablized to a large extent. The energy difference is only about 2.1 kcal/mol between protonated **A-H**$^+$ and the **3-H**$^+$ one. This two species are compatible.

c) Mass spectrometric experiments
Experimental details:

Experiments were carried out using a Synapt G2-S high definition mass spectrometer with an electrospray ion source. The instrument was held at a capillary voltage of 3.0 kV. The instrument has a quadrupole mass filter for the selection of parent ions. Mass selected ions enter into a linear ion trap cell which is filled with argon. The pressure is approximately 8×10^{-3} mbar. After collision, a reflectron time-of-flight (TOF) detector was used to determine the masses. The ion source block and nitrogen desolvation gas temperatures were set to 100 ºC and 300 ºC. For a given ion of interest, the elemental composition was confirmed by examination of the associated isotope envelopes in the source spectra. Collision induced dissociation was employed to analyze structural fragments.

The samples were diluted to millimolar by methanol (acid 0.37mM, [Cp*IrCl$_2$]$_2$ 0.37mM), and then infused into ESI source at a flow rate of 5 μl min^{-1} through a syringe pump.
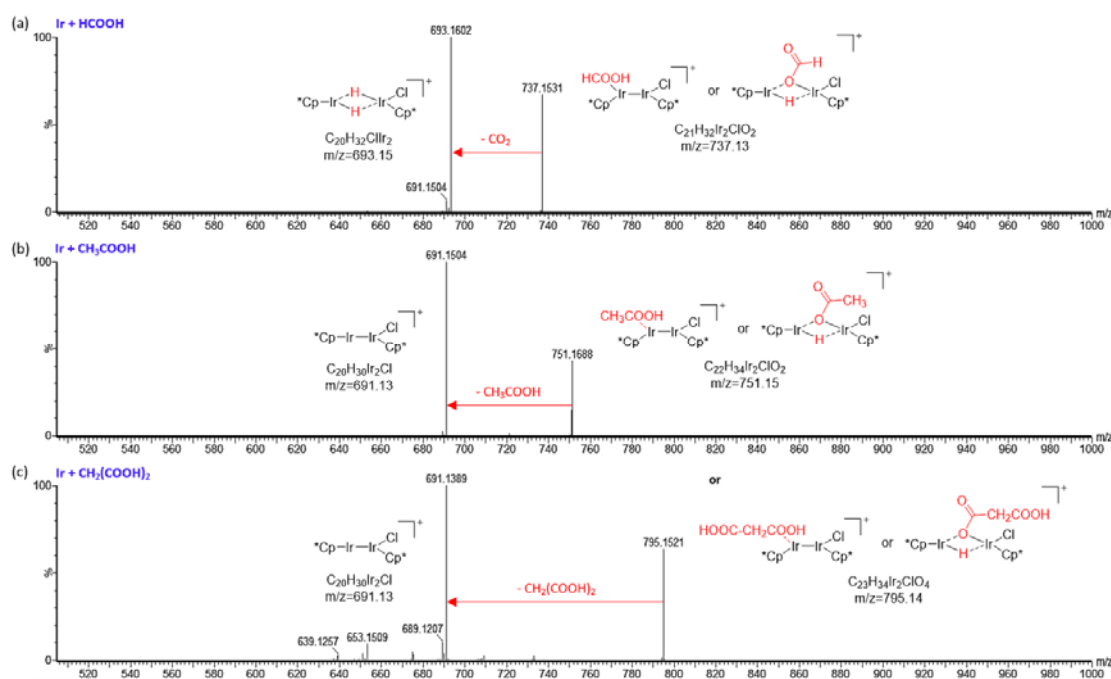

Figure S2 **(a)** CID mass spectrum of ion m/z=737.15 at U$_{trap}$=10 V (E=0.52 eV) in 1:1 mixture of [Cp*IrCl$_2$]$_2$ with HCOOH solution. **(b)** CID mass spectrum of ion m/z=751.17 at U$_{trap}$=12 V (E=0.61 eV) in 1:1 mixture of [Cp*IrCl$_2$]$_2$ with CH$_3$COOH solution. **(c)** CID mass spectrum of ion m/z=795.15 at U$_{trap}$=17 V (E=0.81 eV) in 1:1 mixture of [Cp*IrCl$_2$]$_2$ with CH$_2$(COOH)$_2$ solution. (Ar is used as collision gas.)

A series of methanol solutions of a 1:1 mixture of [Cp*IrCl$_2$]$_2$ (0.37 mM) with HCOOH, CH$_2$COOH, CH$_2$(COOH)$_2$ acids were subjected to ESI-MS analysis respectively. Peaks m/z=737, 751 and 795 were observed in the three different samples, were preliminarily assigned to [Cp*$_2$Ir$_2$ClCHO$_2$]$^+$, [Cp*$_2$Ir$_2$ClC$_2$H$_4$O$_2$]$^+$, [Cp*$_2$Ir$_2$ClC$_3$H$_4$O$_4$]$^+$. To further characterize the structure of these ions, collision induced dissociation (CID) were performed. After collision with Ar, ions m/z=751 and 795 in CH$_3$COOH, CH$_2$(COOH)$_2$ solutions dissociate one molecule CH$_3$COOH and CH$_2$(COOH)$_2$ respectively (Figure S2(b) and (c)). However, the ion m/z=737 in

HCOOH system, loses a molecule CO_2 fragment (Figure S2(a)). This may give a hint why HCOOH failed for this reaction while with the addition of CH_3COOH or $CH_2(COOH)_2$ can afford the target product. The preliminary mass spectrometric result shows different reaction patterns in the presence of different acids, which may relate to the role of acid. Further comprehensive mechanistic studies are undergoing and will be covered in a following full paper.

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Reviewer #2 (Remarks to the Author):

After reviewing the revised manuscripts, I am satisfied with all revisions made by authors. I will recommend the acceptance of this article in its current form.