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A diversity-oriented synthesis of bioactive benzanilides *via* a regioselective C(sp²)–H hydroxylation strategy†

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A diversity-oriented synthesis of bioactive benzanilides *via* C(sp²)–H hydroxylation has been studied. Different regioselectivity was observed with Ru(II) and Pd(II) catalysts. The reaction demonstrates excellent regioselectivity, good tolerance of functional groups, and high yields. A wide range of *ortho*-hydroxylated-benzanilides can be readily synthesized with excellent regioselectivity *via* this new synthetic strategy. Computational investigations revealed that the regioselectivity was controlled mainly by both steric and electronic factors. Steric effects determine the regioselective outcomes in the Ru-catalyzed reaction, while electronic effects are dominant in the Pd-catalyzed reaction.

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Introduction

Hydroxylated benzanilides are an important class of chemicals used frequently in pharmaceuticals and agrochemicals (Fig. 1).¹ The position of the hydroxyl group, *i.e.* at the *ortho*-position in either the benzoyl or the aniline moiety, may determine dramatically different bio-activities. For example, in a DNA-PK inhibitor the hydroxyl group is on the benzoyl segment, but it is on the aniline ring in a rotamase inhibitor. Synthesis and screening of small molecule libraries containing diverse hydroxylated benzanilides will be a highly valuable means of identifying potent hits in early drug discovery. With target-oriented synthesis, hydroxylated benzanilides can be prepared *via* the condensation of carboxylic acids with amines, but this strategy usually suffers from limitations such as poor availability of starting materials, difficult reaction procedures, low yields and the formation of side products (Scheme 1b).² For example, when salicylic acid reacts directly with aniline, interaction of the carboxyl and phenolic hydroxyl groups could lead to a significant side reaction. Diversity-oriented synthesis (DOS) is a strategy for rapid access to relatively small libraries of organic molecules with an emphasis on skeletal diversity.³ Structurally diverse compound libraries are highly valuable for

drug discovery; to date, many important small molecule modulators of challenging biological targets have been identified from DOS-derived compound libraries.

Due to the challenges in reactivity and selectivity however, the use of C–H functionalization in DOS is still uncommon.⁴ In the last decade, direct functionalization of sp² C–H bonds by transition-metals emerged as a powerful method for generating new C–O bonds.^{5,6} Among these studies, the ruthenium(II)-catalyzed C–H oxygenation of benzamides^{5n,6b} and the palladium(II)-catalyzed C–H oxygenation of anilides^{5s,5t,6a} are the most relevant (Scheme 1a). Although the impressive progress of C–H hydroxylation and other oxidations have provided a toolbox for the functionalization of benzanilides, there are challenges that remain for directed C–H hydroxylation in terms of regioselectivity, scope and practicality of these protocols. For instance, the knowledge about regioselective C–H hydroxylation of substrates containing two or more arenes and its corresponding applicable utility in the preparation of biologically important molecules is still surprisingly limited. Inspired by the diversification of bioactive molecules *via* the controlled chemical or enzymatic oxidation of C–H bonds reported by Baran,⁷ we envisioned that the diversity-oriented synthesis *via* regioselective C–H hydroxylation for bioactive benzanilides could be achieved using different metal catalysts (Scheme 1c). In this paper, we report the development of Pd(II)- or Ru(II)-catalyzed regioselective C–H hydroxylation of benzanilides, which provides a convenient method for the preparation of diverse *ortho*-hydroxylated benzanilide derivatives. This regioselective strategy as a means of accessing different types of hydroxylated benzanilides directly from benzanilide substrates is particularly attractive and depends highly on the practicality of such chemical processes. Our computational studies revealed that the distinct regioselectivity outcomes are dictated by both steric and electronic factors, and highlighted the importance of the

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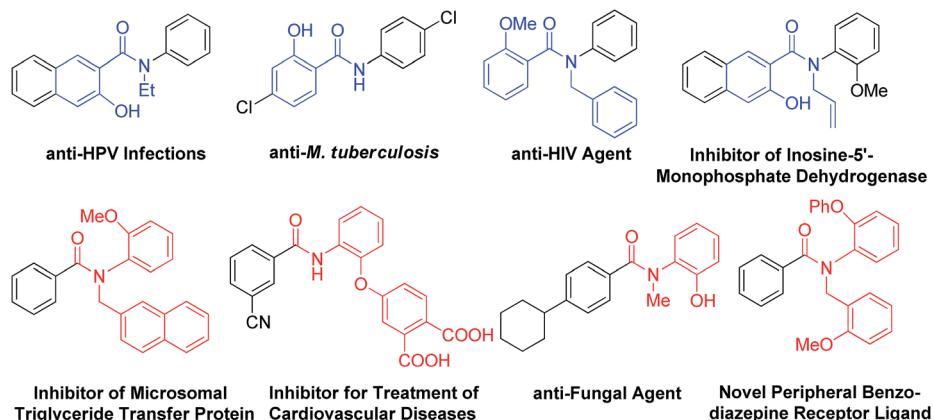
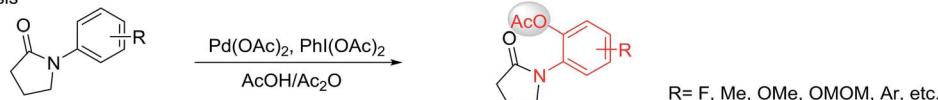


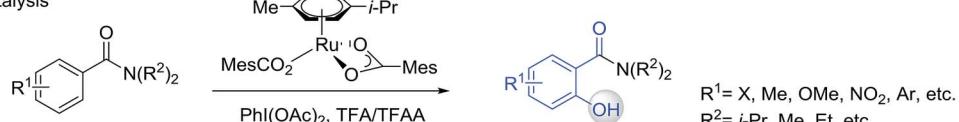
Fig. 1 Biologically important molecules containing hydroxylated benzamides

a) previous works

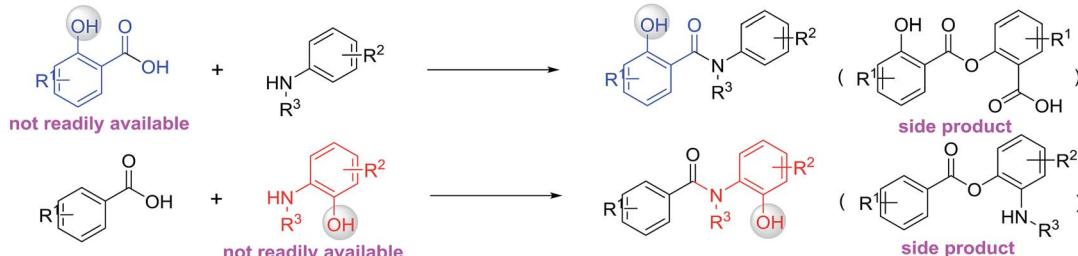
Palladium catalysis



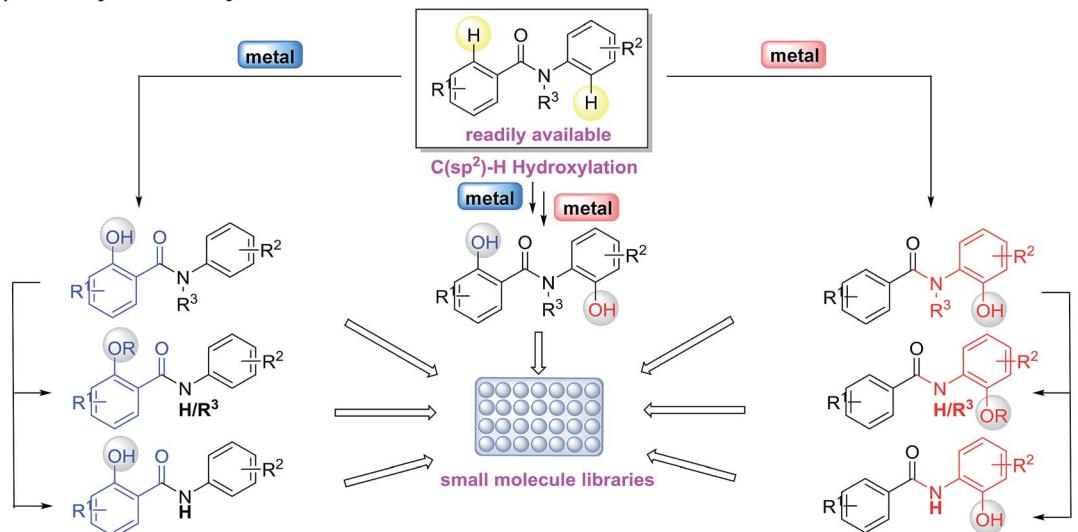
Ruthenium catalysis



b) target-oriented synthesis



c) diversity-oriented synthesis



Scheme 1 A diversity-oriented synthesis for accessing hydroxylated benzamides via C(sp²)–H functionalization.

coordination geometries that metal ions prefer for regioselectivity.

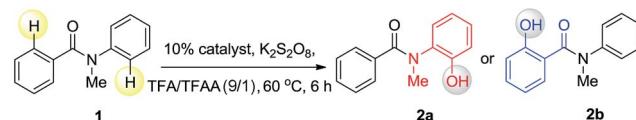
Results and discussion

Since different metals form various cyclic metal intermediates, sometimes *via* different mechanisms,^{8,9} we speculated that regioselective C–H activation of benzanilides could occur with metal catalysts by attacking distinct *ortho* protons. In such cases, regioselective C–H hydroxylation may be realized with suitable reagents and oxidants. We started our investigation with substrates containing two arenes. As shown in Table 1, to test this hypothesis, we initiated a model study with *N*-methyl-benzanilide (**1**) in the presence of various transition metal catalysts in a TFA (trifluoroacetic acid)/TFAA (trifluoroacetic anhydride) cosolvent system with different oxidants, including $\text{PhI}(\text{OAc})_2$, NaIO_4 , HIO_3 , selectfluor, $\text{Na}_2\text{S}_2\text{O}_8$, $\text{K}_2\text{S}_2\text{O}_8$, H_2O_2 , *etc.* (for details, please see the ESI[†]). We discovered that among the screened catalysts, only rhodium, ruthenium and palladium can provide significant amounts of phenol products. In contrast, other metal catalysts including Cu, Fe, Ni, Ag, Au and Co, failed to promote the transformations under the same reaction conditions (entries 1–13). Further analysis of the experimental results revealed an interesting phenomenon that rhodium and ruthenium catalysts always gave the same

regioselective products. However, different regioselectivity outcomes were observed under palladium catalysis. For example, when a Ru(II) or Rh(II) catalyst was used, hydroxylation occurred *ortho* to the carbonyl group to give compound **2b** (entries 17–18). In the presence of a Pd(II) catalyst, hydroxylation occurred *ortho* to the acylated amine group to afford the hydroxylated product **2a** (entry 21). In terms of the efficiency of metal catalysis, Pd(II) and Ru(II) were found to be better than Rh(II). Various Pd(II), Rh(II) and Ru(II) catalysts were examined in this reaction, and a consistent regioselectivity with varying product yields was observed (entries 14–23). Among the tested oxidants, $\text{K}_2\text{S}_2\text{O}_8$ was noted to be superior over others. Generally, 0.1 equiv. of the Ru(II) or Pd(II) catalyst was enough to effectively promote the reaction. Typically the reaction will proceed to completion in TFA/TFAA within 10 hours, in a clean manner, with 2.0 to 3.0 equivalents of the oxidant.

Having established the experimental studies of the regioselectivity results using Ru(II) or Pd(II), we further examined the substrate scope and robustness of this method. As illustrated in Fig. 2 and 3, a broad range of phenol derivatives (**3a**–**3f**, **4a**–**4z**) were prepared in good to excellent yields. The *ortho*, *meta* and *para*-substituted aryl groups, as well as the electron withdrawing and electron donating functional groups (halide, methyl, ester, CF_3 , and nitro groups) are well tolerated and only specific regioselective phenol products were obtained. As

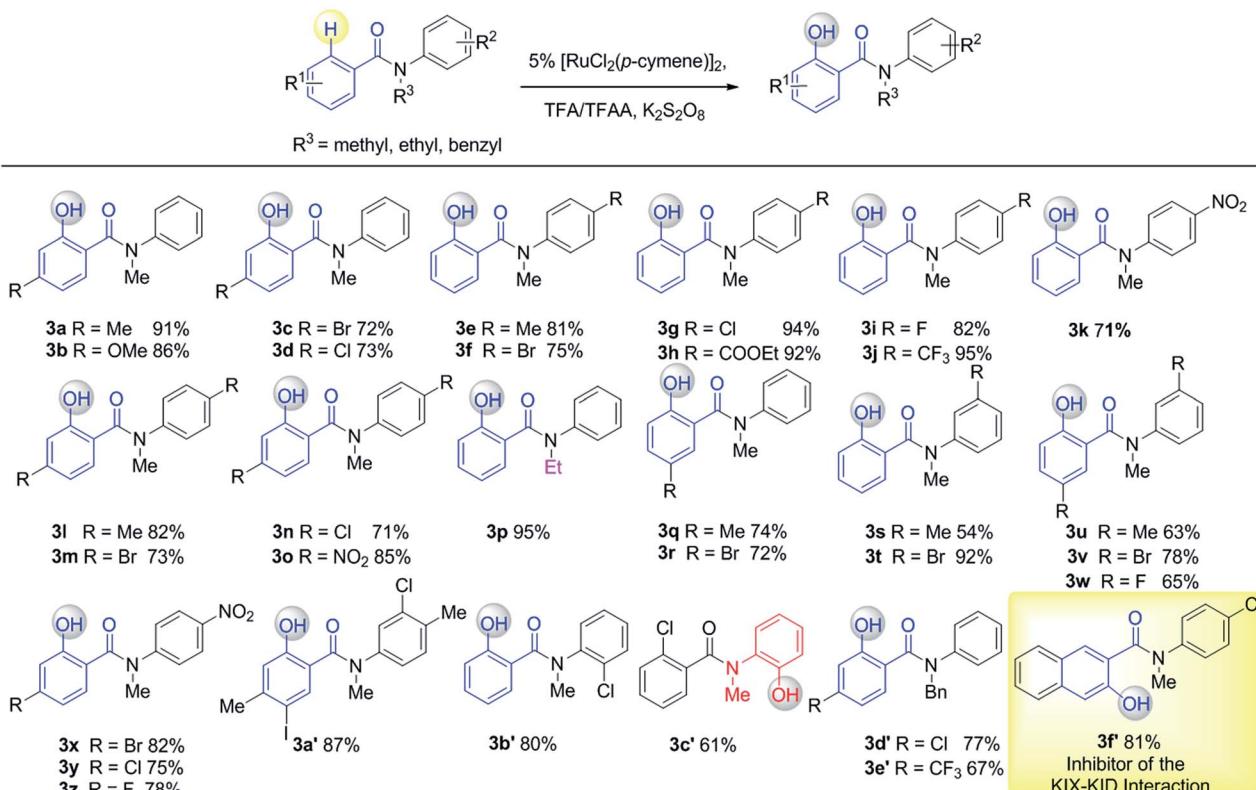
Table 1 Regioselectivity with different metals on *N*-methyl-benzanilides



Entry	Catalyst	2a yield ^a (%)	2b yield ^a (%)
1	FeBr_3	<5	<5
2	$\text{Fe}(\text{OAc})_2$	<5	<5
3	$\text{Co}(\text{OAc})_2$	<5	<5
4	CoF_3	<5	<5
5	Bis(1,5-cyclooctadiene)nickel	<5	<5
6	Bis(triphenylphosphine)nickel dichloride	<5	<5
7	CuI	<5	<5
8	$[\mu\text{-Bis(diphenylphosphino)methane}]\text{Au}_2\text{Cl}_2$	<5	<5
9	AuCl	<5	<5
10	$\text{Mn}(\text{OAc})_2$	<5	<5
11	NbCl_5	<5	<5
12	(1,5-Cyclooctadiene)(methoxy)iridium	<5	<5
13	$\text{Ce}(\text{SO}_4)_2 \cdot 4\text{H}_2\text{O}$	<5	<5
14	$\text{Rh}_2(\text{TFA})_4$	<5	43
15	$[(\text{C}_6\text{H}_5)_3\text{P}]_3\text{RhCl}$	<5	8
16	$[\text{Cp}^*\text{RhCl}_2]_2$	<5	<5
17	$\text{Rh}_2(\text{OAc})_4$	<5	37
18	$[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$	<5	93 ^b
19	$[(\text{C}_6\text{H}_5)_3\text{P}]_3\text{Ru}(\text{CO})(\text{Cl})\text{H}$	<5	73
20	$[(\text{C}_6\text{H}_5)_3\text{P}]_3\text{RuCl}_2$	<5	60
21 ^c	$\text{Pd}(\text{OAc})_2$	70 ^b	<5
22 ^c	$\text{Pd}(\text{acac})_2$	67	<5
23 ^c	$\text{Pd}(\text{TFA})_2$	57	<5

^a Conversion ratio. ^b Isolated yield. ^c 0.5 h.



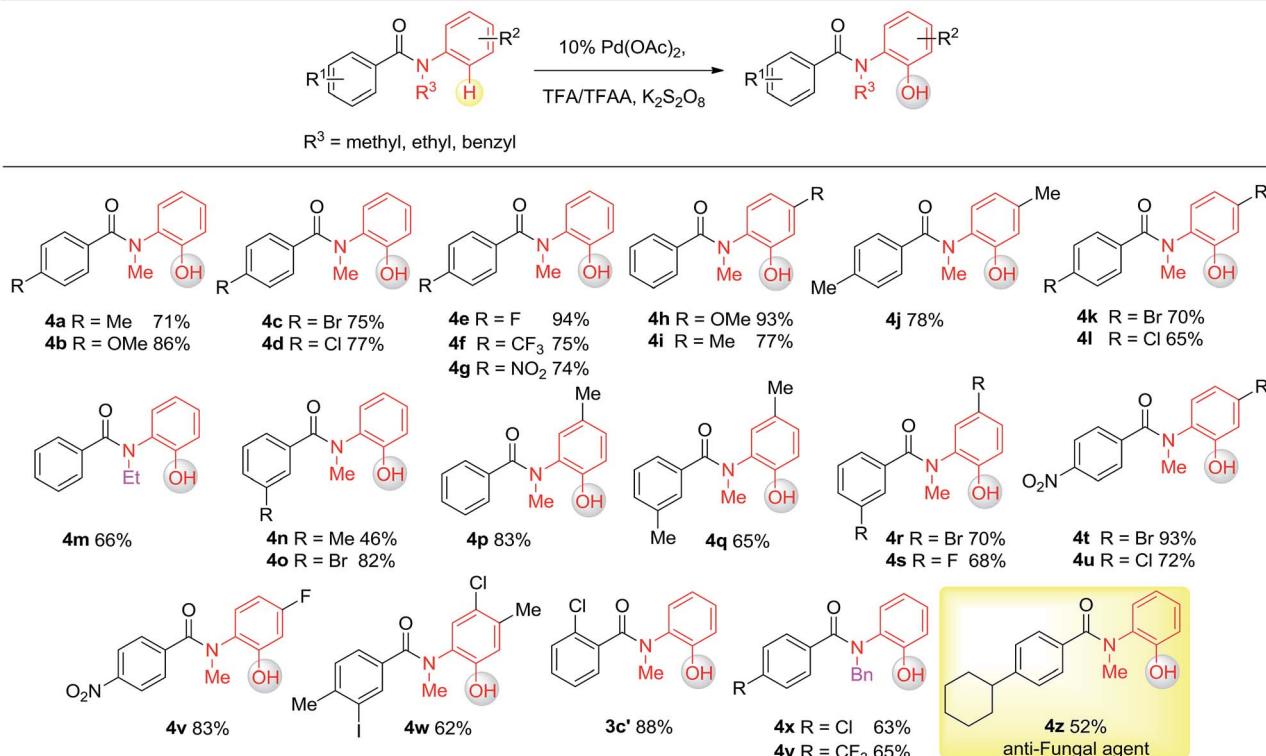
Fig. 2 Substrate scope of Ru(II) in C(sp²)-H hydroxylation (isolated yield).

a result of steric effects, *meta*-substituted substrates always gave only one regioisomer formed by hydroxylation from the less hindered side. In all cases of ruthenium and palladium catalysis, the corresponding regioselective phenol products can be consistently obtained. A special example is about 2-chloro-*N*-methyl-*N*-phenylbenzamide. When it was used as the substrate, hydroxylation took place at the *ortho*-position of the acetyl-amino group in the presence of either a ruthenium or palladium catalyst to afford the hydroxylated product **3c'**. The steric hindrance from the *ortho*-substituted chlorine group may account for this result. To our delight, *N*-ethyl-benzanilide and *N*-benzyl-benzanilides can be used in place of *N*-methyl-benzanilides as well and provide the desired phenol products (**3p**, **3d'**, **3e'**, **4m**, **4x**, **4y**) with excellent reactivity and regioselectivity similar to those of the methyl counterparts. *Ortho*-hydroxylated benzanilides with unprotected N-H can be readily prepared by regioselective deprotection of the corresponding *ortho*-hydroxy-*N*-alkyl-benzanilides (Scheme 2). Thus, our “hydroxylation and deprotection” strategy can readily afford two kinds of *ortho*-hydroxylated benzanilides, which also represent an important class of bioactive molecules.¹⁰ As shown in Scheme 2, a one-step deprotection procedure involving acidic or hydrogenation conditions readily removes the *N*-benzyl group to furnish the *ortho*-hydroxylated-N-H-benzanilide product **5a**, **5b** and **5c** respectively.

To demonstrate both the practicality and effectiveness of this method for large-scale synthesis, we prepared **2b** and **2a** on a gram scale under the optimized reaction conditions with only

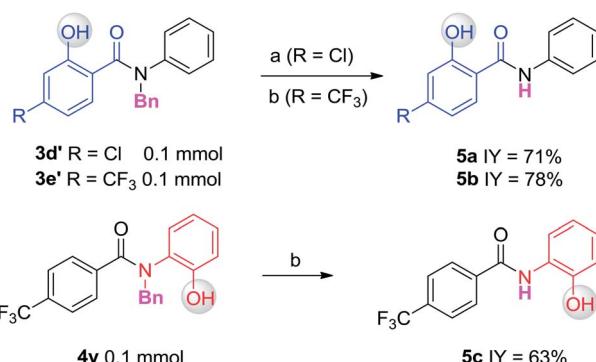
2.5 mol% $[\text{RuCl}_2(\text{p-cymene})]_2$ or 5 mol% $\text{Pd}(\text{OAc})_2$ catalyst (Scheme 3). In comparison to conventional approaches requiring 2-(alkylamino) phenol derivatives or substituted benzoyl peroxides, which are generally relatively expensive, our method, with its operational simplicity and ready availability of starting materials, is advantageous for rapid access to these molecules. The applicability of this reaction was further demonstrated in the synthesis of biologically important molecules. As exemplified in Fig. 2 and 3, Ru(II)-catalyzed C–H hydroxylation can smoothly transform the substrate, *N*-(4-chlorophenyl)-*N*-methyl-2-naphthamide, in a good yield into the hydroxylated product **3f**, which represents a class of effective inhibitors of the KIX–KID interaction.^{11a} KID is the kinase-inducible domain in the cyclic AMP response element binding protein (CREB). KIX is the KID-interacting domain in CREB-binding protein (CBP). This type of compound has been identified as a cell-permeable inhibitor of the KIX–KID interaction which directly binds to KIX. Our method provides a convenient way by which to synthesize this type of naphthol derivative with excellent chemoselectivity and this synthetic strategy might present a new opportunity to develop novel transcription-based cancer therapeutic agents. Similarly, a one-step protocol *via* a Pd(II)-catalyzed C–H hydroxylation could easily convert 4-cyclohexyl-*N*-methyl-*N*-phenylbenzamide into the fungicide^{11g} **4z**. The preparation of this type of molecule with traditional methods has always suffered from poor selectivity and low yields.

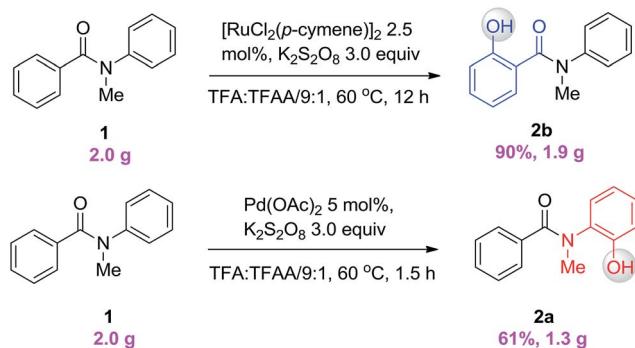
One of our long-term goals is to synthesize a diverse collection of *ortho*-hydroxylated benzanilide derivatives *via* a diversity-

Fig. 3 Substrate scope of Pd(II) in C(sp²)-H hydroxylation (isolated yield).

oriented synthesis strategy, which can be further screened in different biological assays to facilitate early drug discovery. To illustrate the utility of our new synthetic method for the preparation of a focused small molecule library of benzylides, 20 different benzylides can be rapidly constructed from two common precursors within 3–4 steps. As exemplified in Scheme 4 and 5, a wide variety of bioactive benzylides can be tolerated and prepared under our hydroxylation conditions. For instance, the basic structures of **2b** and **2a** prepared according to our method have been demonstrated to have enzymatic de-esterification activity^{11b} and anti-fungal activity.^{11c} The *ortho*-

hydroxylated N–H-benzylide product **5b** is an analogue of a compound for anti-parasitic treatment.^{11d} The hydroxyl group can be further transformed into an alkyl ether (**6a**, **6c**, **6i**), aryl ether (**6d**, **6e**) or derivatives of morpholine (**6n**) or oxazole (**6m**). These molecules have different reported bioactivities in the literature. For example, the ether compounds **6b**, **6d** and **6e** are analogues of a lifespan-altering compound,^{11e} a virion infectivity factor (VIF) inhibitor that blocks viral replication^{11f} and an inosine-5'-monophosphate dehydrogenase (IMPDH) inhibitor,^{11d} respectively. When the proton on the amide nitrogen of an *ortho*-hydroxylated benzylide is substituted by a benzyl group, and the hydroxyl group is transformed to a methoxyl group, the corresponding benzylide becomes an anti-HIV agent^{11c} (**6g**). This type of structure serves as a central scaffold in the study of non-nucleoside reverse transcriptase inhibitors. The synthesis of **6g** can be started from a simple benzylide through a sequential benzylation–hydroxylation–methylation transformation. Remarkably, as shown in Scheme 4, dihydroxylated products can be easily obtained *via* a two-step hydroxylation manipulation using two different catalysts (Pd and Ru). Among them, the di-methoxylated product **6i** has anti-rice blast activity^{11g} and the di-hydroxylated N–H-benzylide product **6k** is an analogue of an antimicrobial agent.^{11h} Besides N-alkyl-benzylides, useful analogues of N–H-benzylide compounds, can also be readily prepared by this method. We smoothly obtained three types of analogues from one precursor, *N*-(2-hydroxyphenyl)-4-(trifluoromethyl)benzamide (**5c**). Among them, one is a modulator of the CCR-receptor (**6l**). As is known, chemokines play an important role in immune and

Scheme 2 Deprotection of *ortho*-hydroxylated N-benzyl benzylides.



Scheme 3 Gram-scale synthesis of *ortho*-hydroxylated *N*-methylbenzamides.

inflammatory responses in various diseases and disorders, including asthma and allergic diseases; CCR receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of these disorders and diseases.¹⁴ Using the same starting material, an analogue of a compound used in sunscreen, 2-(4-(trifluoromethyl)phenyl)benzo[*d*]oxazole¹⁵ (**6m**), was readily prepared *via* an intramolecular dehydration reaction. The third obtained benzamide is a P2X4 receptor antagonist analogue (**6n**), which is a derivative of morpholine. It inhibits the ATP-induced calcium influx in 1321N1 astrocytoma cells stably transfected with the human P2X4 receptor, and it has potential as a drug for the treatment of neuropathic pain and neurodegenerative diseases.¹⁶ To our pleasure, all these C–H hydroxylation reactions demonstrated excellent regio- and chemoselectivity, as well as reactivity.

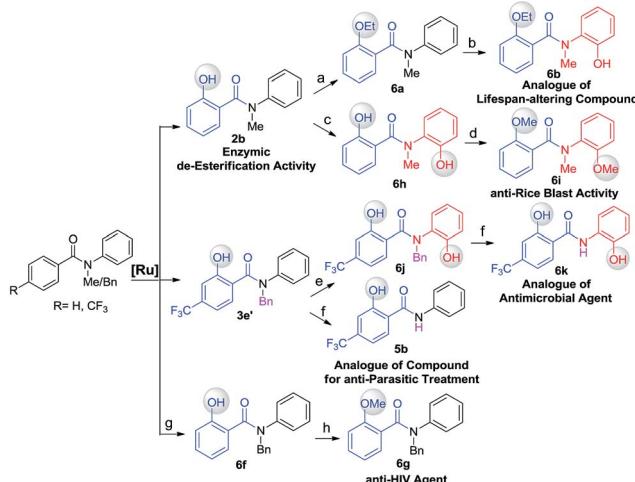
The phenomenon that Ru and Pd have distinct regioselectivity is of great interest. Mechanistic studies were then

performed to reveal the origin of the selectivity. Our previous kinetic isotope effect (KIE) studies of similar reactions revealed that C–H activation is involved in the rate-determining step.⁶ To examine whether C–H activation is also the critical step to determine the selectivity for this work, inter- and intramolecular isotope effect measurements were conducted in parallel (Scheme 6). All KIE values are greater than 2, confirming that C–H activation is involved in the rate-limiting step of these two transformations. No H/D exchange was observed for these substrates, indicating that C–H bond activation is irreversible and determines the selectivity.

As shown in Scheme 7, *N*-methyl-benzanilide has two types of directing groups (DGs), amide ($-\text{CONMeR}$) and acylated amine ($-\text{NMeCOR}$). The transition states of the two types of DGs involve a 5-membered ring and a 6-membered ring, respectively. According to our previous studies of the priority order of various DGs,¹² the acylated amine group ($-\text{NR}^1\text{COR}^2$) has a higher priority than the amide group ($-\text{CONR}^1\text{R}^2$) for Pd catalysts. This would lead to the hydroxylation on the aniline side and our present experimental data is consistent with this finding. However, the priority ordering of these two DGs is contrary for the Ru catalyst, which causes the different regioselectivity for C–H activation. In light of these results, a density functional theory (DFT) study was conducted.¹³

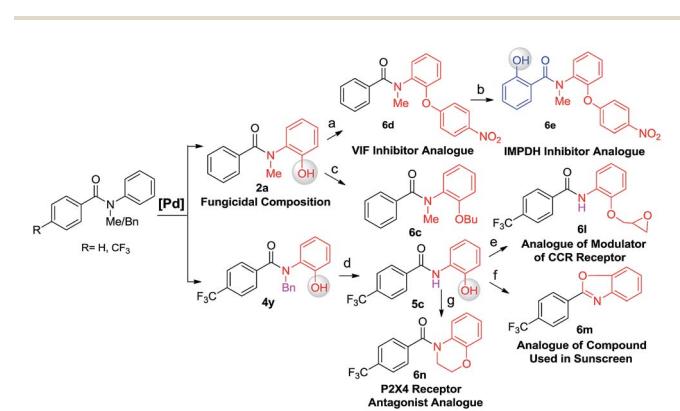
Recent mechanistic studies on carboxylate-assisted transition-metal catalyzed C–H activation suggested that the concerted metalation–deprotonation (CMD) mechanism with an inner- or outer-sphere base was the most favorable mechanism.¹⁴

The initial steps of forming active catalysts are shown in Fig. S1 and S2.[†] Given the fact that the C–H activation step determines the regioselectivity, here we focus on the C–H activation step. Four critical transition structures, **TS1**–**TS4**, are depicted in Fig. 4. The calculation is consistent with the experimentally observed regioselectivity. Early kinetic and computational studies demonstrated that C–H activation



Reaction conditions: a) Et₃Li 4 eq, t-BuOK 4 eq, THF, 25 °C, 6 h, 79%. b) Pd(OAc)₂ 15 mol%, K₂S₂O₈ 2.5 eq, TFA: TFAA/9:1, 60 °C, 1.5 h, 56%. c) Pd(OAc)₂ 15 mol%, K₂S₂O₈ 2.0 eq, TFA: TFAA/9:1, 60 °C, 1 h, 60%. d) MeI 4 eq, t-BuOK 4 eq, THF, 25 °C, 12 h, 70%. e) Pd(OAc)₂ 10 mol%, K₂S₂O₈ 2.5 eq, TFA: TFAA/9:1, 60 °C, 2 h, 67%. f) Pd/C, H₂, AcOH, 70 °C, 4 h. g) [RuCl₂(*p*-cymene)]₂ 5 mol%, K₂S₂O₈ 3.0 eq, TFA: TFAA/9:1, 60 °C, 5 h, 96%. h) MeI 3.0 eq, t-BuOK 3.0 eq, THF, 25 °C, 12 h, 89%.

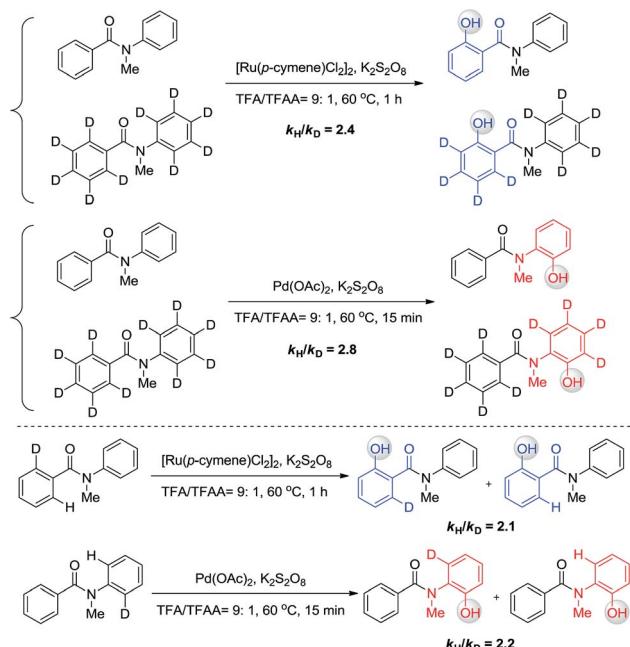
Scheme 4 A useful compound analogue library prepared *via* diversity-oriented synthesis (with [Ru] as a catalyst).



Reaction conditions: a) *p*-fluoronitrobenzene 1.1 eq, K₂CO₃ 5.0 eq, DMF, 50 °C, 5 h, 84%. b) [RuCl₂(*p*-cymene)]₂ 5 mol%, K₂S₂O₈ 3.0 eq, TFA: TFAA/9:1, 60 °C, 6 h, 63%. c) BuLi 8 eq, t-BuOK 8 eq, THF, 25 °C, 16 h, 60%. d) Pd/C, H₂, AcOH, 70 °C, 4 h. e) alkyl bromide 4.0 eq, Cs₂CO₃ 3.0 eq, CH₃CN, 25 °C, 10 h, 77%. f) *p*-toluenesulfonic acid monohydrate 3.2 eq, toluene, Ar, 110 °C, 3 h, 60%. g) 1,2-dibromoethane 8.0 eq, K₂CO₃ 20 eq, acetone, 60 °C reflux, 5 h, 64%.

Scheme 5 A useful compound analogue library prepared *via* diversity-oriented synthesis (with [Pd] as a catalyst).





Scheme 6 Kinetic isotope effect.

catalyzed by $\text{Pd}(\text{OAc})_2$ is electrophilic in character.¹⁵ When reacting in trifluoroacetic acid (TFA), the dissociation of one TFA ligand makes the Pd center even more electrophilic. Therefore, electron-donating substituents on the arene group facilitate the reaction.^{1,15} For *N*-methyl-benzanilide, the more electron rich Ar^2 is expected to undergo C–H activation preferentially. Indeed, for the Pd catalyst, the regioselectivity is dominated by the electronic effect (see Fig. 4, **TS1** and **TS2**), which is also consistent with the priority ordering of the DGs,¹² and using the dissociated acid ligand as an outer-sphere base to deprotonate the C–H bond might be the most favorable mechanism (see ESI†).¹⁶ However, the use of a Ru catalyst results in the hydroxylation at Ar^1 . Inspection of the geometries illustrates that steric factors may be controlling the regioselectivity, overwhelming the electronic effect in this reaction with Ru. Unlike the square planar geometry in the case of Pd(II), Ru(II) adopts a “piano stool” geometry, which is more crowded. Due to the steric repulsion from the *N*-methyl group, Ar^1 and Ar^2 both twist away from the amide plane. In **TS4**, the constraint of the newly formed metallocycle and the repulsion of the *N*-methyl group

force Ar^2 to be closer (2.31 Å) to the *p*-cymene cap and as a result, **TS4** is less favorable than **TS3** by 2.2 kcal mol^{−1}.

To further examine the hypothesis that the steric effect overrides the electronic effect in the Ru-catalysis transition state, we replaced the *N*-methyl group with H to reduce the steric repulsion. As illustrated in Fig. 5, the steric constraint in **TS6** is largely diminished in the absence of the *N*-methyl group and preferred activation of Ar^1 via **TS5** was predicted.

Experiments with benzanilides were then conducted to verify the computational prediction. Hydroxylation indeed occurs on the *ortho*-position of the aniline (Ar^1) with either the Pd(II) or Ru(II) catalyst (Scheme 8). However, the yield of these reactions with *N*-benzanilides is unsatisfactory under the current conditions. Accordingly, we recommend the protocol in Scheme 2 for the synthesis of *ortho*-hydroxylated *N*-H-benzanilides.

In a further test to verify the role of repulsion between the substrate and the *p*-cymene cap, additional model calculations were performed. The *p*-cymene cap was replaced by smaller ligands or deleted to eliminate the steric factor and the corresponding energies were calculated. In these cases, the regioselectivity is reversed (see Fig. S3† for more details), and consequently, the steric repulsion between the cap and the aryl ring is thought to play an important role in the regioselectivity. This highlights the importance of considering the coordination geometries preferred by a metal center when performing

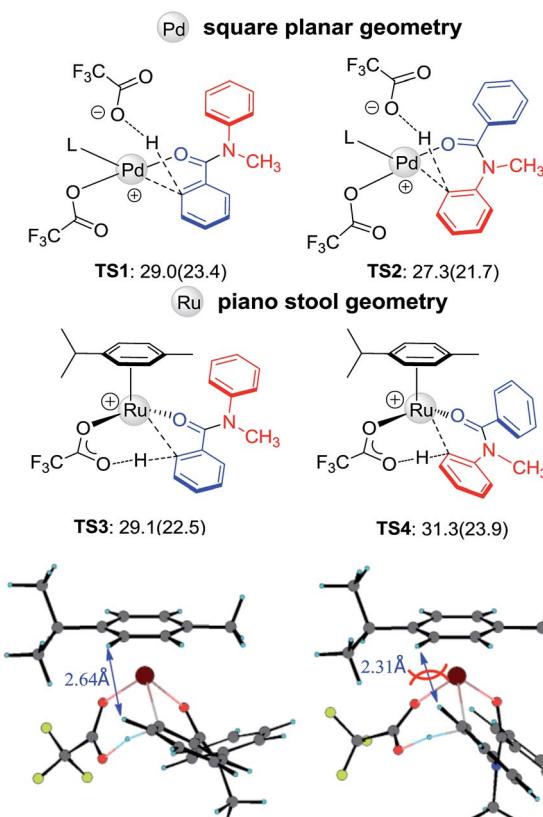
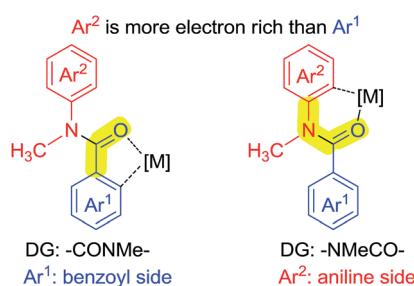


Fig. 4 The structures and free energies of activation of the Ru- and Pd-catalyzed C–H activations on Ar^1 and Ar^2 sides for *N*-methyl-benzanilide; electronic activation energies (in kcal mol^{−1}) are in parentheses (L = *N*-methyl-benzanilides).

Scheme 7 Two types of DGs of *N*-methyl-benzanilide.

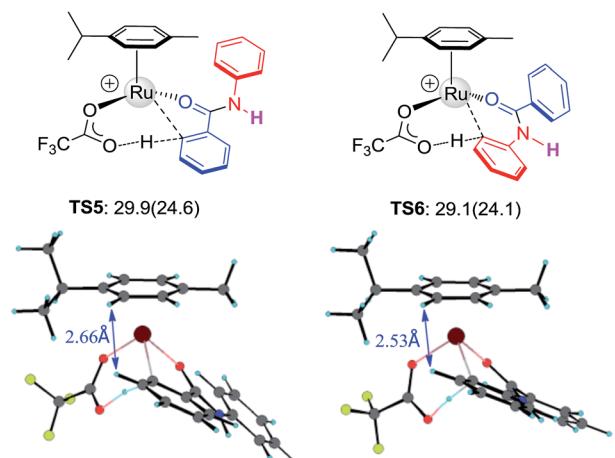
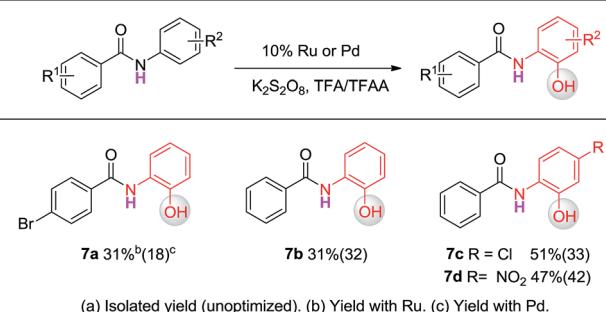


Fig. 5 The structures and free energies of activation of Ru catalyzed C-H activation on Ar^1 and Ar^2 sides for N-H-benzanilide; electronic activation energies (in kcal mol^{-1}) are in parentheses.



Scheme 8 Ortho-hydroxylation of N-H-benzanilides.^a

carboxylate-assisted transition-metal catalyzed C-H activation reactions.¹⁷

Conclusions

We have demonstrated the regioselective *ortho*-hydroxylation of *N*-alkyl-benzanilides catalyzed by Pd(II) or Ru(II) to access two distinct *ortho*-hydroxylated regio-isomers. When Pd(II) is employed as the catalyst, the hydroxylation occurs on the phenyl ring of aniline. In contrast, a reversed regioselective product will be obtained in the presence of the Ru(II) catalyst. This method has been found to be generally useful for the preparation of a broad range of *ortho*-hydroxylated-*N*-alkyl-benzanilides with excellent regio-selectivity. Related *ortho*-hydroxylated benzanilides can be easily obtained by subsequent deprotection. These two types of compounds have been widely used in the initial stages of drug discovery. The reaction demonstrates excellent regioselectivity and good functional group tolerance, and proceeds with high yields. Its utility has been well exemplified in further synthetic applications of bioactive molecules. Further computational studies revealed that both steric and electronic factors account for the origin of the different regioselectivity between Ru(II) and Pd(II). Moreover,

the coordination geometries that a metal center prefers are important for the regioselectivity. Further studies into the scope and the application of this reaction are currently in progress in our laboratory.

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