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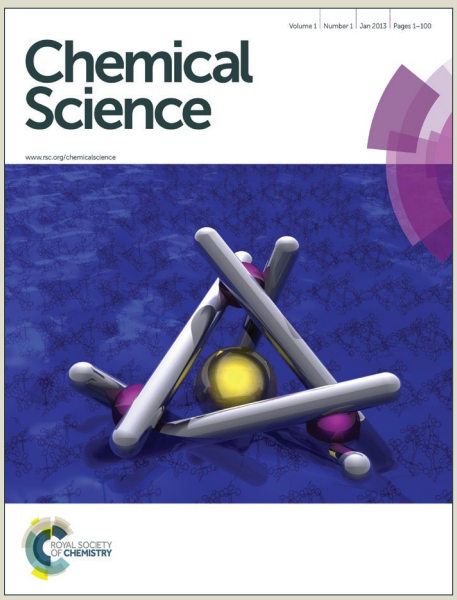

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ARTICLE

Directing Group Assisted *meta*-Hydroxylation by C–H Activation

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

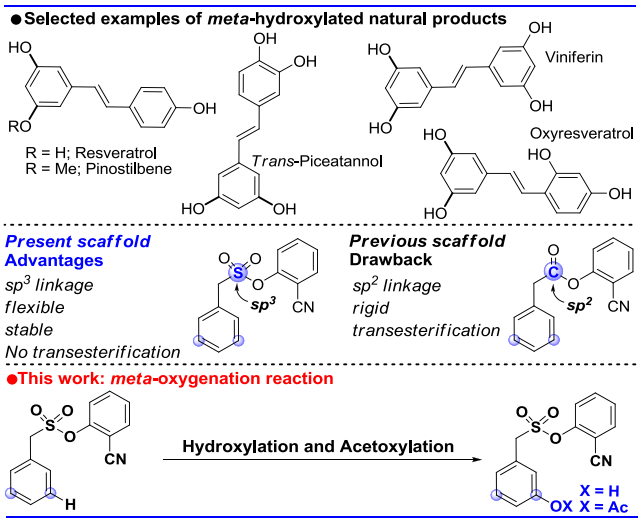
DOI: 10.1039/x0xx00000x
www.rsc.org/

Abstract: *Meta*-hydroxylated cores are ubiquitous in natural products. Herein, we disclose first template assisted *meta*-hydroxylation reaction. Experimental and *in silico* studies helped us to gain valuable mechanistic insights, including the role of hexafluoroisopropanol (HFIP) solvent, during C–H hydroxylation. The reactive intermediates, prior to the C–H activation, have been detected by spectroscopic techniques. Additionally, the C–O bond formation has been extended to *meta*-acetoxylation. Preparation of phase II quinone reductase activity inducer and a resveratrol precursor illustrated the synthetic significance of the present strategy.

Introduction

The ability to transform carbon-hydrogen bond to a carbon-heteroatom bond is highly important owing to its involvement in late-stage functionalization of complex natural products, pharmaceuticals and agrochemicals.[1] An effective strategy in this domain is yet to achieve its full potential due to the inherent problem of selectivity and reactivity of the carbon-hydrogen bond.[2] Although the concept of directing-group (DG) assistance resolves the issue of selective functionalization of the proximal C–H bond,[3] distal *meta*-C–H bond is difficult to activate.[2b, 4] Hence the intrinsic electronic bias of the substituted core has been utilized to promote the *meta* C–H functionalization.[5] In order to reach the remote *meta* C–H bond the idea of traceless directing group, transient mediator and the concept of H-bonding has been utilized.[6] However, regardless of the functionalization, template assisted direct *meta*-C–H bond activation requires involvement of large strained metallacycle intermediate. Therefore the success relies on the perfect design of the directing group (DG) linkage, coordinating site and the choice of metals. In 2012, the pioneering work by Yu and co-workers has demonstrated the feasibility of the hypothesis using U-shaped template with tethered –CN directing group.[7] The concept was explored in various arylamine, benzylamine, cinnamic acid, phenol, benzyl alcohol and phenyl acetic acid scaffolds by the same group to elucidate the directing group assisted C–C and C–O bond formation *via* olefination, arylation, alkylation and acetoxylation reactions.[7-8] Further, the concept of optimal coordination by –CN directing group has been extended by Tan group, our group and recently by Li group towards benzylsilyl, benzylsulphonyl, phenyl acetic acid and phenylethyl amine derivatives.[9] Despite significant progress in template assisted *meta* selective C–C bond formation, generation of C–X (heteroatom) bond at *meta* position is still in its infancy.

Following our initial report in *meta*-olefination of the phenylacetic acid core (Scheme 1),[9b] arylmethane sulphonyl moiety was identified to mitigate trans-esterification issues noted in earlier instance.[9c] Moreover *meta*-C–O bond formation with phenylacetic acid was found to be problematic. Therefore, we planned a *meta*-hydroxylation reaction with an arylmethane sulphonyl core as the model substrate. Despite successful acetoxylation of arylamine,[8c] benzylamine and indoline scaffolds[8d] by Yu and coworkers, single-step *meta*-hydroxylation protocol is yet to be reported.



Scheme 1. Overview of the present work

Results and Discussions

Our initial attempts of direct hydroxylation failed owing to the intolerance of the cyano directing group under strong oxidizing conditions (Table 1). Hence we envisioned installing an oxygenating group under a mild oxidizing condition followed by its *in-situ* hydrolysis.[10] With $PhI(TFA)_2$ (4 equiv.) as the hydroxylating agent,[11] *N*-formyl-glycine (For-Gly-OH, 25 mol%) as the ligand for $Pd(OAc)_2$ (10 mol%) in HFIP solvent, the desired *meta*-hydroxylated compound was obtained in 78% (isolated, 74%) yield and excellent selectivity (>20:1).

With the optimized condition, the scope of the reaction was explored (Table 2). Electron rich alkyl substituted arenes were hydroxylated with good yield and excellent selectivity (**1b**, **1c** and **1g**). Steric crowding in the close vicinity of the *meta*-C–H bond was found to affect the formation of the palladated intermediate. Moving from –Me (**1b**) to –*i*Pr (**1c**) as the *para* substituent, yield

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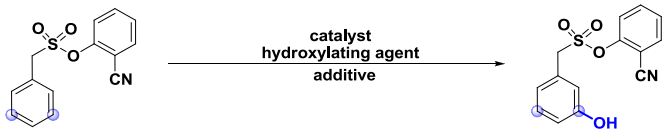
Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

declined from 77% to 63%. In disubstituted systems, replacing chloro (**1h**) with bromo (**1i**) enhances the selectivity towards less hindered *meta*-C–H bond (**1h**, 65% and **1i**, 63%). Groups such as –OPh, –OCF_3, –OMe were also tolerated.

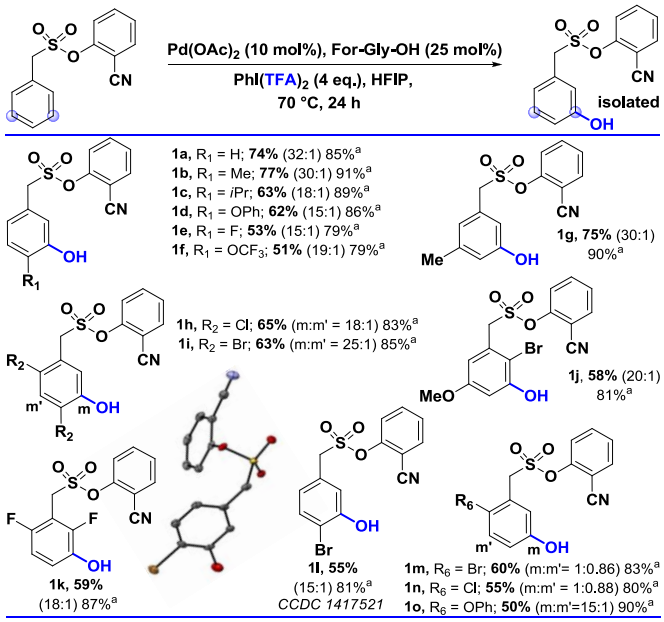
Table 1. Different approaches of hydroxylation[12]



	Catalyst[a]	-OH source	Yield
1	$PdCl_2$/ $Pd(OAc)_2$	TBHP (4 eq.)	0
2	$PdCl_2$	H_2O_2 (4 eq.)	0
3	$PdCl_2$	NHPI (2 eq.)	0
4	$Cu(OAc)_2$	$(PhCO)_2O$ (2 eq.), HFIP (1 mL)	0
5	$PdCl_2$ / $Pd(OAc)_2$	TEMPO (2 eq.)	0
6	$Cu(OAc)_2$	TBAI(2 eq.), Ag_2CO_3(2 eq.)	0
7	$PdCl_2$	$K_2S_2O_8$ (2 eq.), CF_3COOH (0.5 mL)	0
8	$Pd(OAc)_2$	$Na_2S_2O_8$ (2 eq.); Dioxane (1 mL)	0
9[b]	$Pd(OAc)_2$	$PhI(TFA)_2$(4 eq.),$(CF_3CO)_2O$	11
10	**$Pd(OAc)_2$**	**$PhI(TFA)_2$ (4 eq.), HFIP (1 mL)**	**78**

[a] *Catalyst loading 10 mol%;* [b] *0.5mL of $(CF_3CO)_2O$ added; 70 °C was maintained for all the reactions; All the reactions were performed in 0.2 mmol scale*

Table 2. Scope of *meta*-hydroxylation[13]

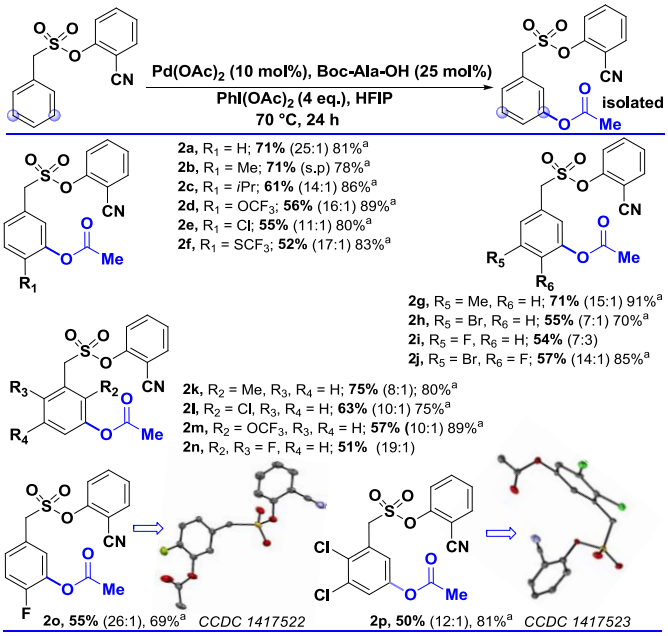


[a] *These yields are based on the recovered starting material*
All the reactions were performed in 0.2 mmol scale with $Pd(OAc)_2$ (0.1 equiv.), For-Gly-OH (0.25 equiv.), $PhI(TFA)_2$ (4 equiv.), HFIP (1 mL.). All the selectivity are (meta:others) obtained from the crude reaction mixtures using 1,3,5-trimethoxybenzene as reference. (m:m').

Interestingly, changing the acetoxylating agent from $PhI(TFA)_2$ to $PhI(OAc)_2$ led to the formation of *meta*-acetoxylated compound as the sole product. Accounting for the importance of the *meta*-acetoxylated compounds, the protocol was optimized and the scope was explored. For *meta*-acetoxylation, *N-tert*-butyloxycarbonyl-alanine (Boc-Ala-OH) was found to be the best ligand for palladium. A similar type of reactivity trend was observed in acetoxylation as that of hydroxylation (Table 3).

Notably, under the standard one-pot approach no dihydroxylation or diacetoxylation product was detected. Although the hydroxyl groups are known to direct the metal to the proximal C–H bond, however no such difunctionalization was observed under the present reaction condition.

Table 3. Scope of *meta*-acetoxylation[13]

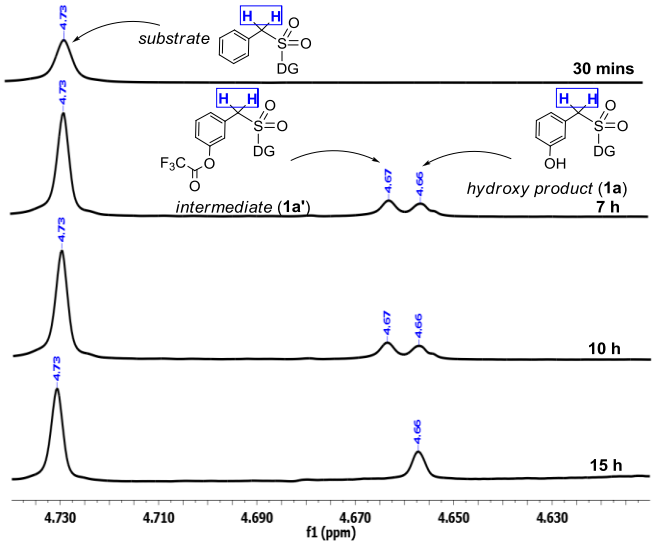


[a] *These yields are based on the recovered starting material*
All the reactions were performed in 0.2 mmol scale with $Pd(OAc)_2$ (0.1 equiv.), Boc-Ala-OH (0.25 equiv.), $PhI(OAc)_2$ (4 equiv.), HFIP (1 mL.) All the selectivity are (meta:others) obtained from the crude reaction mixtures using 1,3,5-trimethoxybenzene as reference.

Arguably, the difference in ligand environment, competitive coordination with the –CN and hindered deprotonation of the phenol under mild acidic nature of the reaction mixture alleviates the scope of undesired functionalization on the product.[14]

Intermediate detection:

The interesting switch of hydroxylation to acetoxylation upon changing the –R on $PhI(OOCR)_2$ from $-CF_3$ to $-CH_3$ can be justified by the reduced electrophilicity of the ester carbonyl in acetate as compared to that in trifluoroacetate which disfavors the hydrolysis and thus remain as an acetoxylated product. This observation is additionally supported by computational study (*vide infra*).

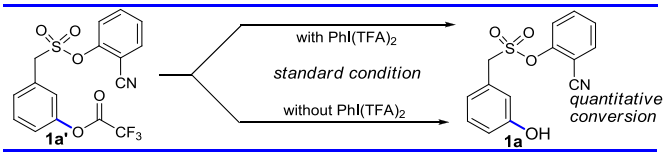


[a] *reactions were performed with 1.5 equiv. of $PhI(TFA)_2$*

Scheme 2. Reaction profile of *meta*-hydroxylation.

Moreover the quantitative conversion of independently synthesized *meta*-trifluoroacetoxylated substrate to *meta*-hydroxy compound under the standard reaction condition (Scheme 3)

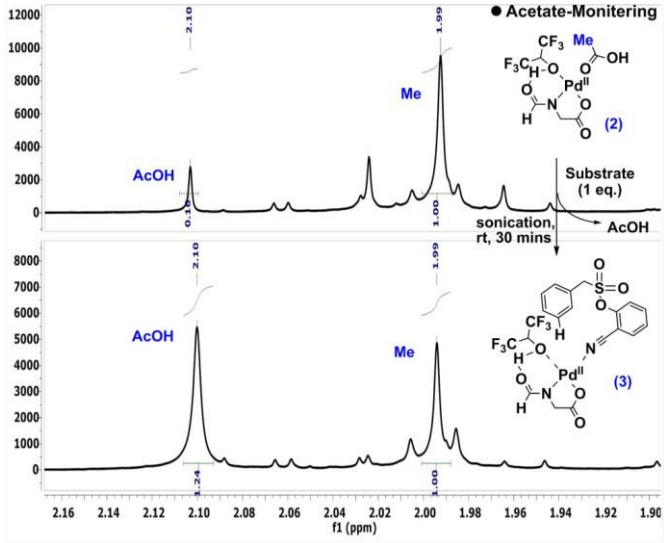
supported our initial hypothesis of hydroxylation strategy.[12] Furthermore, the intermediacy of the trifluoroacetoxylated compound as hydroxyl precursor has been intercepted through NMR study (Scheme 2).



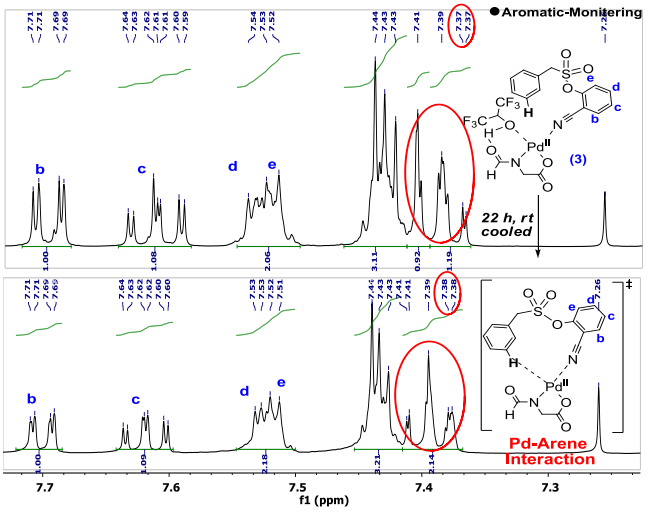
Scheme 3. Generation of hydroxyl compound via hydrolysis

Mechanistic study:

During the optimization of the reaction conditions, HFIP and *N*-protected aminocarboxylic acid ligand were found to be indispensible. To gain better insights on the mechanistic complexity, the reaction was monitored by NMR study. Interestingly, in the presence of stoichiometric $Pd(OAc)_2$ and ligand, the inclusion of the substrate intensified the acetic acid ($-CH_3$) peak, which indicates the release of acetic acid from the metal complex (Scheme 4).[12]



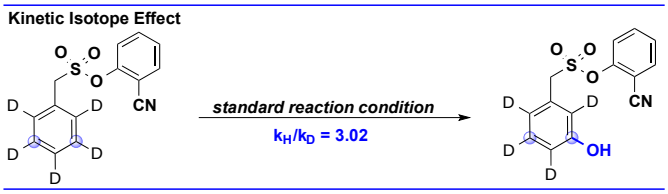
Scheme 4. Detection of acetate release[10]



Scheme 5. Evidence in support of Pd–arene interaction

Upon standing, the splitting pattern of the target aromatic ring was found to be disturbed (Scheme 5). Control experiments revealed that the palladium is essential for such splitting variation in aromatic region. Such an observation can be visualized as the weak interaction within the substrate and palladium, likely the CN-anchored one, which eventually leads to the C–H activation.

The interaction between the palladium and the substrate could be observed from the variation in the C–N bond stretching frequency as well. Upon addition of stoichiometric $Pd(OAc)_2$ to the substrate, the –CN peak position shifted from 2237 cm^{-1} to 2247 cm^{-1}, which further shifted to 2250 cm^{-1} upon addition of stoichiometric amount of ligand. Moreover solvated (MeOH and MeCN) For-Gly-OH ligated palladium species could be identified through mass spectroscopy.



Scheme 6. Determination of kinetic Isotope effect

All these observations pointed towards a facile interaction of the substrate, ligand and HFIP with palladium centre under ambient temperature. Despite these interactions, no desired product was formed at room temperature. This could be indicative to the fact that the C–H activation and the ensuing steps are more energy demanding.

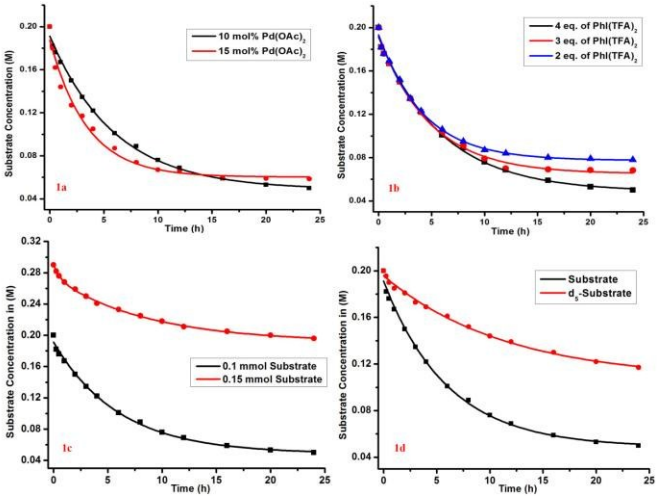
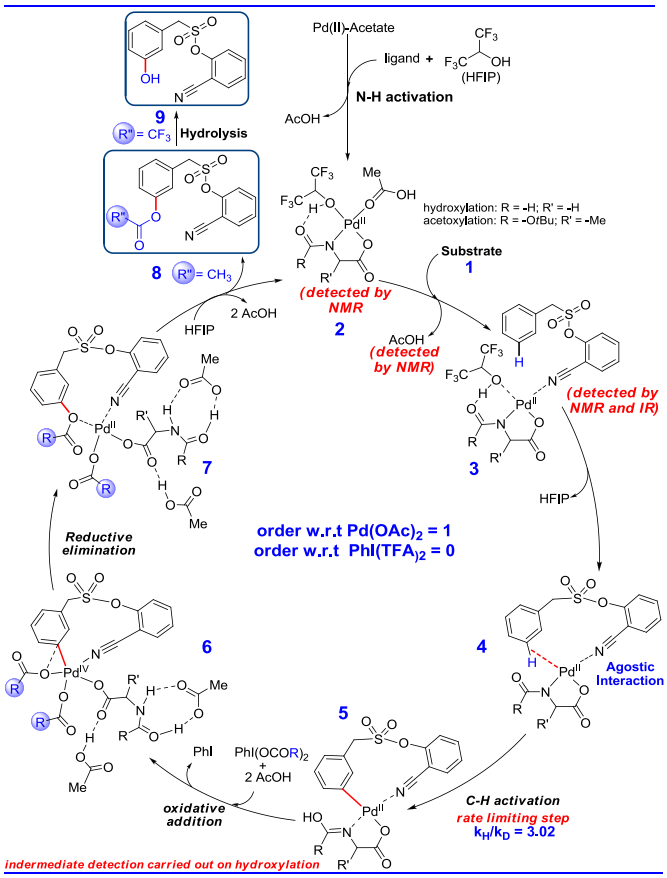


Figure 1. Order determination: *(**1a**) Overlay of reaction profile with 10 mol% and 15 mol% Pd; (**1b**) Reaction profile with different $PhI(TFA)_2$ loading. The reactions were performed in 0.1 mmol substrate, 10 mol% Pd, 25 mol% ligand and 0.5 mL of HFIP with the variation in $PhI(TFA)_2$ only as 2 eq., 3 eq. and 4 eq. (**1c**) Order determination w.r.t to substrate (order =1). Reaction are done in 0.1 and 0.15 mmol scale (**1d**) Determination of kinetic isotope effect (k_H/k_D = 3.02). Reactions are done with model substrate and d_5-substrate in 0.1 mmol scale. In Fig 1c and 1d all the reactions are performed with 10 mol% catalyst, 25 mol% ligand, 4 equiv $PhI(OTFA)_2$ and 0.5 mL/0.1 mmol scale of HFIP at 70 °C.*

The kinetic study showed a first-order rate dependency on the palladium and substrate whereas a zero-order dependency was observed for $PhI(TFA)_2$(Figure 1).[12] The isotope labelling experiment showed a high value of kinetic isotope effect (KIE = 3.02) (Scheme 6). Such a high value of KIE unambiguously establishes C–H activation as the rate limiting step.

DFT Calculation:

Guided by these experimental observations, we have also conducted density functional theory computations to arrive at a plausible mechanistic pathway (Scheme 7). It is worth mentioning that *meta* selective olefination pathway has been computationally investigated jointly by Yu, Wu and Houk groups illustrating the role of *N*-protected amino acid in remote C–H activation.[15] However the *meta* selective C–O bond formation reaction is yet to be addressed using *in-silico* studies. Contextually, DFT studies were carried out using the SMD/M06/6-31G** level of theory to locate key intermediates and transition states involved in the catalytic cycle.[16] Two ligands, namely For-Gly-OH and Boc-Ala-OH were used in our computational study.



Scheme 7. Plausible mechanism

First, different likely active species were examined by varying the ligand combinations around the Pd(II). The deprotonation of the carboxyl and the amino group of the ligand by the Pd-bound acetates led to the formation of an amino acid chelated Pd(II) intermediate (**b**; Figure 2),[17] and labile acetic acid ligands on Pd-center. Experimentally HFIP was found to be vital for the title reaction. Hence, solvent HFIP was probed to study its potential influence on the energetics of the reaction. Notably, the HFIP binding, as in intermediate **2**, was 1.5 kcal/mol lower than the corresponding acetic acid binding.[18] This prediction is in accord to our NMR identification of intermediate **2**. The active species generated through the binding of the amino acid ligand on Pd(II) participated in the catalytic cycle as described below. The major mechanistic steps were consist of (a) substrate uptake through ligand exchange, (b) ligand-assisted C–H activation, (c) oxidative addition to $PhI(OCOR)_2$, and (d) reductive elimination leading to the C_{aryl}–O bond formation (Scheme 7).

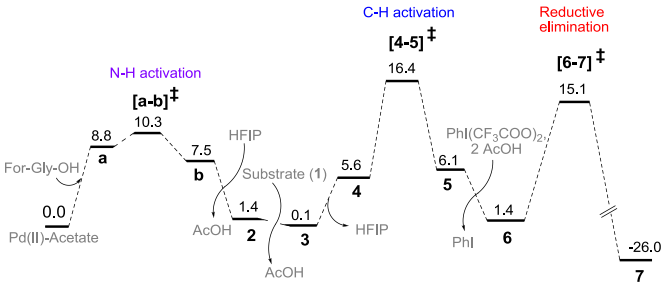


Figure 2. Gibbs free energy profile (kcal/mol) of the *meta* hydroxylation obtained at the SMD/M06/6-31G**, LANL2DZ(Pd) level of theory.

The substrate binding through the cyano group has been considered to direct palladium to the *meta* C–H bond as in intermediate **3**. Although intermediate **3** could have either a neutral acetic acid or a HFIP coordination, HFIP was found to be moderately preferred.[19] Among various possibilities of ligand assisted C–H activation, the abstraction of the C_{aryl}–H proton by the amino acid ligand (Figure 3) was found to be much more preferred (by 4.8 kcal/mol) over the generally proposed acetate-assisted C–H activation.[20]

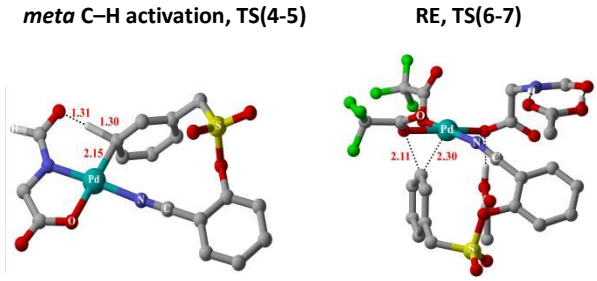
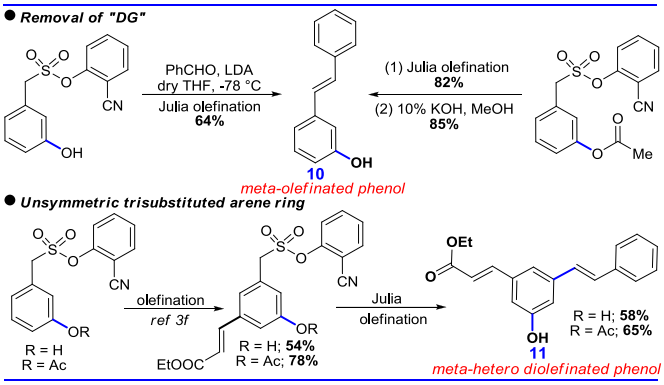


Figure 3. Transition states geometries of two critical steps involved in the *meta* hydroxylation. Select hydrogen atoms are only shown (distances are in Å)

The palladated aryl thus formed underwent oxidative insertion to yield a penta-coordinate Pd(IV) intermediate **6**. In the following vital step, reductive elimination (RE) led in the formation of C_{aryl}–OCOR bond (R = CH_3 or CF_3). In the most preferred RE transition state, a mono-dentate binding of the amino acid ligand (Figure 3) was found to be more preferred over the chelated form.[21] At this stage of the reaction, uptake of an HFIP could assist the release of the product from the catalyst-product complex (**7**) to regenerate the active species (**2**).[22] More interesting aspect at this juncture is the fate of the resulting acetoxylated or trifluoro-acetoxylated product. Experimental observation suggests that the trifluroacetylated product proceeds to hydrolysis to yield a *meta*-hydroxylated compound whereas the acetylated product continues to remain as it is under identical reaction conditions. The origin of this kind of product distribution is traced to the lower energy transition state for an acid catalyzed hydrolysis in the case of trifluoroacetate.[23]

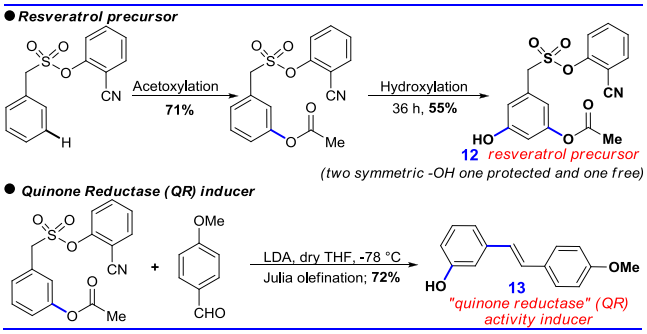
Application:

Although the DG promoted *meta*-C–H functionalization, its removal will be crucial for the synthetic utility of such strategy. In this context, both acetoxylated and hydroxylated compounds formed hydroxyl-stilbene *via* Julia olefination (**10,** Scheme 8). Unsymmetric trisubstituted phenol was also generated using similar approach (**11,** Scheme 8).



Scheme 8. Applicative removal of DG

Further sequential acetoxylation and hydroxylation resulted in the formation of potential resveratrol precursors (**12**). A phase II "Quinone Reductase" (QR) activity inducer (**13**) has also been synthesized using the present protocol (Scheme 9).[24]



Scheme 9. Application of the protocol

Conclusions

In summary, we have developed first template assisted palladium catalyzed direct *meta*-hydroxylation strategy, which was further extended to *meta*-acetoxylation reaction. Interestingly, the variation of R (R = H, F) on the acetoxylating agent $PhI(OOCR_3)_2$ led to the formation of different target molecules under similar reaction conditions. The mechanistic studies revealed an interesting role of the HFIP in the catalytic cycle. The approach has been utilized for the synthesis of unsymmetrically substituted phenols and QR activity inducer to demonstrate the synthetic utility of the protocol.

Acknowledgement

This activity is supported by SERB, India (EMR/2015/000164). Generous computing time from the IIT Bombay supercomputing is acknowledged.

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16. M. J. (a) Full details of the computational methods are provided in the Supporting Information. (b) Gaussian09 quantum chemical suite has been used for the computations. Frisch.
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18. The replacement of both acetic acid ligands by two HFIP molecules is energetically higher than substitution of just one HFIP (See Figures S5 and S10 in the Supporting Information).
19. Link to the results and relative energies of intermediates in the Supporting Information. [Figures S6 and S11].
20. (a) We have also compared the ortho as well as para C–H activation to learn that the meta is energetically most preferred. See Table S19, 20, Figures S4 and S9 in the Supporting Information. (b) D. G. Musaev; A. Kaledin; B.-F. Shi; J. Q. Yu *J. Am. Chem. Soc*. 2011, **134**, 1690.
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