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Mechanistic Insights on Orthogonal Selectivity in Heterocycle Synthesis

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ABSTRACT: Recently we have developed a method for catalytic regioselective synthesis of 2-substituted and 3-substituted benzofurans starting from phenols. The choice of reacting partner, olefin versus α,β–unsaturated acid, is critical to dictate the isomeric product formation. Instances are known where these olefinic partners did not complement each other and yield a similar outcome. In the current work, we have addressed this paradox with emphasis on (a) the origin of orthogonal selectivity, and (b) the key requirements to expect complementary behavior. Experimental and computational studies provided important mechanistic insights. Electrostatic compatibility during migratory insertion and the positioning of the carboxylic acid moiety in catalytic steps are found to exert a paramount impact in determining the regioselectivity. The study offers a predictable single component tuning tool to control the regioselectivity.

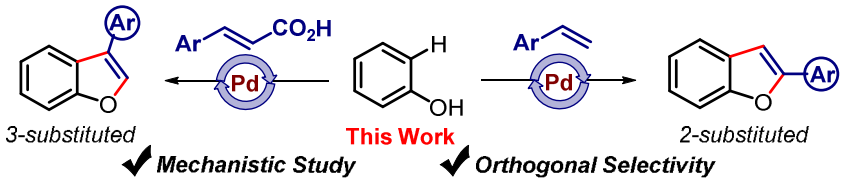
KEYWORDS: Heterocycle • orthogonal selectivity • mechanism• kinetics• computational

INTRODUCTION

Achieving site selective transformation on the reactive functional group is a key goal in organic synthetic chemistry.[1] Preferential formation of an isomer in a competitive environment are largely facilitated by the manipulation of the reaction parameters. In this context, asymmetric synthesis, chemoselective functionalizations, regioselective transformations are explored in great details.[2-5] In comparison to the traditional chemical approach, catalytic routes offer a significantly broader scope of calibration.[6-10] For instance, application of regioselective functionalization of the unsaturated chemical bonds has largely attributed by the development of transition metal catalysts.[1, 11-17] The installation of efficient ligands further expands the scope of fine tuning the selectivity.[18-22] Despite superior selectivity, catalyst dependent selective functionalization techniques are transformation specific and offers a narrow scope of generalization. Furthermore, expensive customized ligands make the scalability less affordable. As an alternative significant amount of effort has been invested to utilize the abundant, economical olefins as the key component to control the regioselectivity in the product.[23-30] In this regard our group has demonstrated regioselective synthesis of heterocyclic cores from olefinic feedstock where the regioselectivity is largely governed by the choice of the olefinic partner.[23, 27]

Heterocyclic units with proper positioning of the substituents are extremely important in the development of functional small molecules and in diversity-oriented synthesis. Benzofurans are one of such prevalent structural motifs found in natural products, pharmaceuticals, agrochemicals and organic materials.[31-39] Over the last two decades several synthetic methods have been developed.[40-50] Generally, heteroannulation of alkynylated and olefinated phenols or arenes are employed to generate functionalized benzofurans.[51-59] Coupling reactions with appropriate prefunctionalized substrates are also known to be effective.[60-62] Recently direct

conversion of simple phenols to benzofurans has been explored.[23, 27-28, 63-68] Our group has demonstrated the formation of 2-substituted benzofurans from phenols by using abundant olefinic feedstock.[23] An orthogonal route for 3-substituted benzofuran synthesis was also developed (Scheme 1).[27] Notably, such regioselective synthesis from simple phenol derivatives is often accompanied by a strained metallacycle formation compounded by a difficult reductive elimination as well as a competitive oxidative product formation.[69-74] Our methods, however, offered excellent yield and selectivity. It was observed that the orthogonal selectivity largely dependents on the choice of the olefinic partners and thus offering a handle to tune a single reactant to adjust the selectivity.



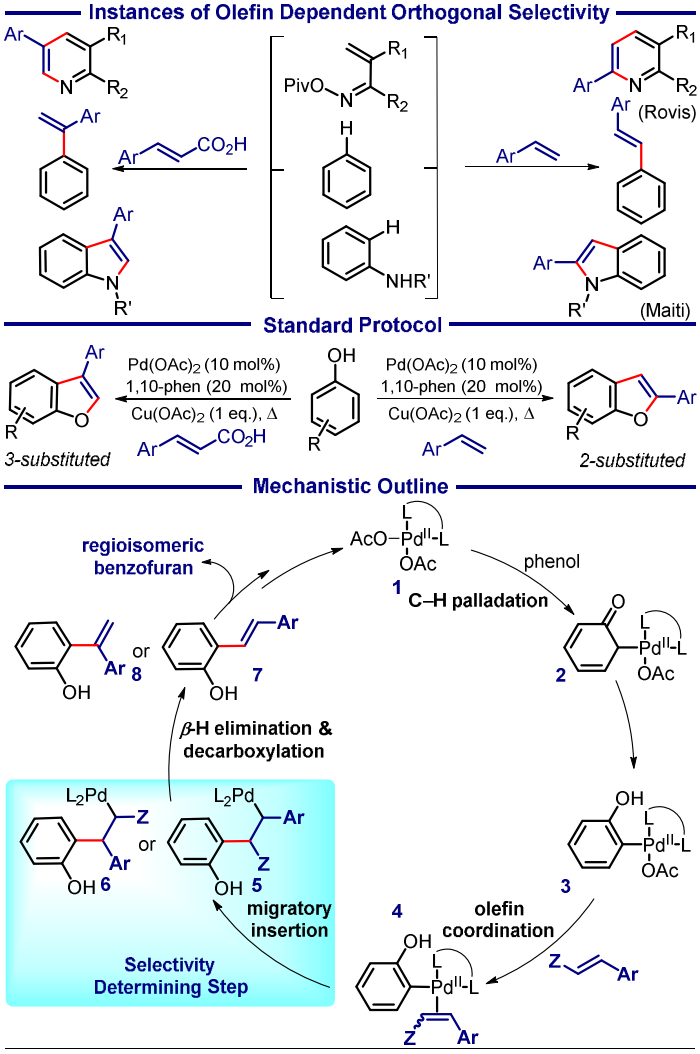
Scheme 1. Orthogonal selectivity in benzofuran synthesis

A similar mode of orthogonal selectivity was obtained for 2- and 3-substituted indole with aniline as the coupling partner.[24, 26] Interestingly, in Fujiwara-Moritani reaction, replacement of olefins by α, β–unsaturated acids generated isomeric branched olefinated products, a challenging target for unactivated coupling partners.[75-76] Further, simultaneous functionalizations at 2- and 3-positions of benzofuran were also realized.[28] Rovis and coworkers reported similar selectivity inversion in the synthesis of 2- and 3-substituted pyridines (Scheme 2).[29-30]

Seemingly, the selection of olefinic partners is critical to the selectivity inversion and can be implemented for the generation of diverse core structures.[77-82] Although electronically olefins and α, β–unsaturated acids are different, instances are known where one acts as an alternative to

other.[25, 80, 83-84] Therefore understanding the mechanistic intricacies of olefin dependent regioselective transformation is essential to gain a predictable control.

In the current work, we have reasoned the essential characteristics of olefin controlled regioselective synthesis of benzofuran heterocycle with emphasis on *(a) the origin of orthogonal selectivity, and (b) the essential requirement for such complementary behavior.* Experimental and computational studies are employed to develop deeper understanding and offer predictable control of regioselectivity.



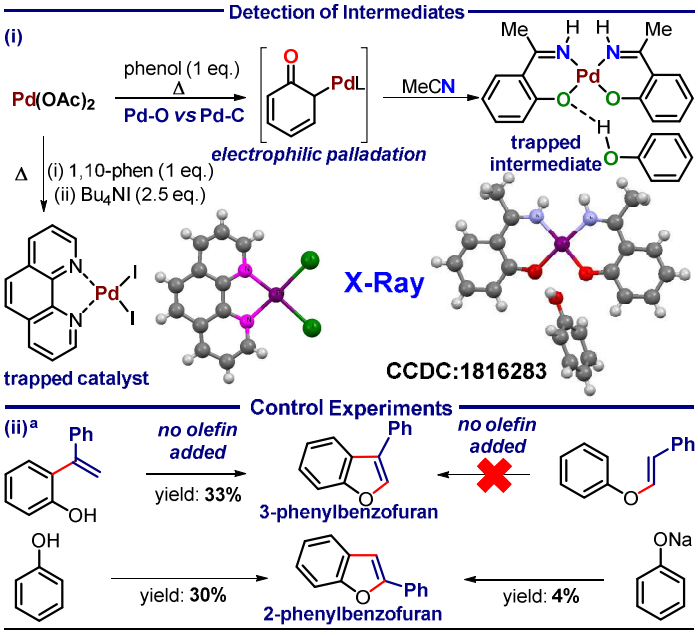
Scheme 2. Overview and key mechanistic steps for benzofuran synthesis.

The key mechanistic features in the formation of benzofuran from phenol can be considered as follows; palladium acetate can first combine with 1,10-phen (L_2) to form the active catalyst (**1**). An *ortho* palladation of phenol in the catalyst-substrate complex can give rise to intermediates **2** and **3**. Subsequent olefin uptake can result in a π-adduct **4** which upon migratory insertion can generate intermediate **5** or **6** depending on the nature of the olefins. Finally, a combination of *β*-hydride elimination, cyclization and aromatization completes the regioselective synthesis of benzofuran. We intend to probe the origin of the mode of migratory insertion between phenol and olefin in **4** as it can be exploited toward harnessing the product regioselectivity.

Formation of Palladated Intermediate:

In presence of 1,10-phen ligand, $Pd(OAc)_2$ is likely to form the $[Pd(phen)]^{II}$ species as the active catalyst (**1**). The proposition of organometallic intermediates in the catalytic cycle is verified by trapping the active catalysts with iodide, in the form of Pd(1,10-phen)I_2 (Scheme 3i). The isolated complex is catalytically active, yet kinetically sluggish due to its stability and thus requires elevated reaction temperature. The active catalyst (**1**) once formed, trends to interact with phenol which is likely to go through a Pd–O or Pd–C(*ortho*) coordination. The formation of later (Scheme 2; **2** or **3**) is confirmed by inserting it to the nitrilic unsaturation of acetonitrile in a square planar complex (Scheme 3i). The coordinating nature of the nitrile group largely attributes to the stability of the complex which is likely to resemble the olefin insertion intermediate (**5** or **6**) of the catalytic cycle. In addition, control experiments suggest that the *ortho*-styrenyl phenol can cyclize to benzofuran whereas vinyl phenyl ether does not (Scheme 3ii).[23] Further, failure of sodium phenoxide as a substrate indicates the Pd–C(*ortho*) species as a favorable reactive intermediate (Scheme 3ii).[23] Moreover, Pd–O connectivity, if formed, can

switch to Pd–C(*ortho*) under the reaction condition.[85] These observations clearly indicate the intermediacy of an *ortho*-palladated species. Arguably phenol is more prone to phenoxide formation, yet softer nature of *ortho*-carbon over phenolic oxygen can provide a better anchoring for palladium. The failure of the phenoxide is largely attributed by the hard-soft mismatch among the phenoxide and palladium center.



[a] *reactions were done under respective standard conditions*

Scheme 3. (i) Detection of intermediates (ii) substrate dependent control experiments

DFT calculations were performed to compare the energetics of Pd–C (*ortho*) and Pd–O bond formation. Calculations suggest that the active catalyst (1,10-Phen)Pd(OAc)$_2$ (**1**) is likely to be formed from Pd(OAc)$_2$ and 1,10-phen (Figure 1).[85-86] As shown in path A in Figure 1, the Pd-bound acetate abstracts the phenolic proton with a concomitant formation of the Pd–C(*ortho*) bond (**2**) *via* transition state **TS(1-2)** with a barrier of 8 kcal/mol. On the other hand, the cleavage of *ortho* C–H bond (from **2** to **3**) involves a higher barrier of 14 kcal/mol (**TS(2-3)**). Subsequent migratory insertion of styrene to the Pd–C(*ortho*) bond of **3** *via* **TS(4-5)** leads to the

formation of *ortho*-olefinated intermediate (**5**) with a barrier of 14 kcal/mol. The formation of **5** is found to be exoergic by 5 kcal/mol and is also characterized experimentally. Alternatively, in path B (Pd–O bond formation) a similar deprotonation of phenol by acetate is a barrierless process forming an intermediate **a** *via* **TS(1-a)**. Despite this initial energetic advantage, the migratory insertion of styrene to form **b** is found to be highly unfavorable by 30 kcal/mol. Moreover, the generation of intermediate **b** is endoergic by 4 kcal/mol. The computed kinetic and thermodynamic features suggest the involvement of an *ortho*-aryl C-olefinated phenol (path A) over O-olefination (path B), which is in coherence with the experimental observations.

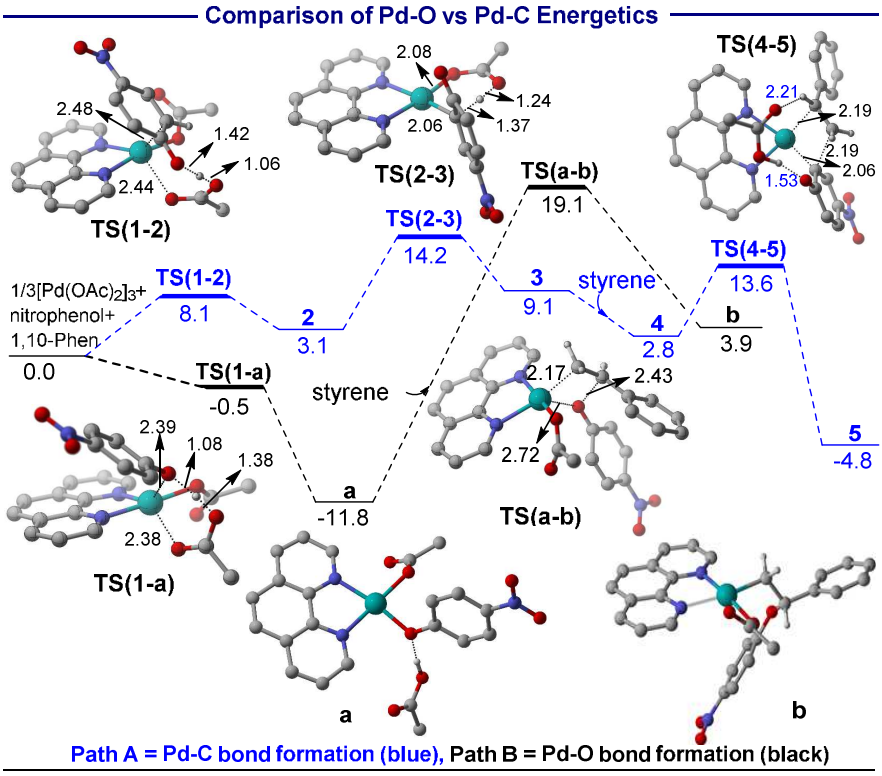
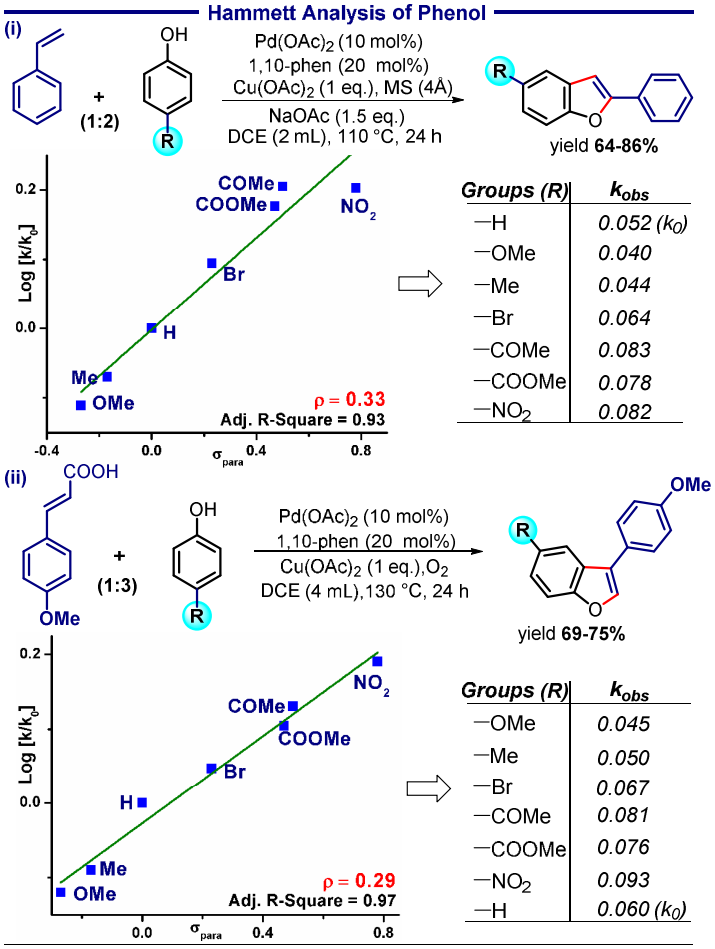


Figure 1. Gibbs free energy (kcal/mol) profile for the formation of intermediate **5** at the $SMD_{(DCE)}$/B3LYP-D3/def2-TZVP//B3LYP/6-31G**,LanL2DZ(Pd).

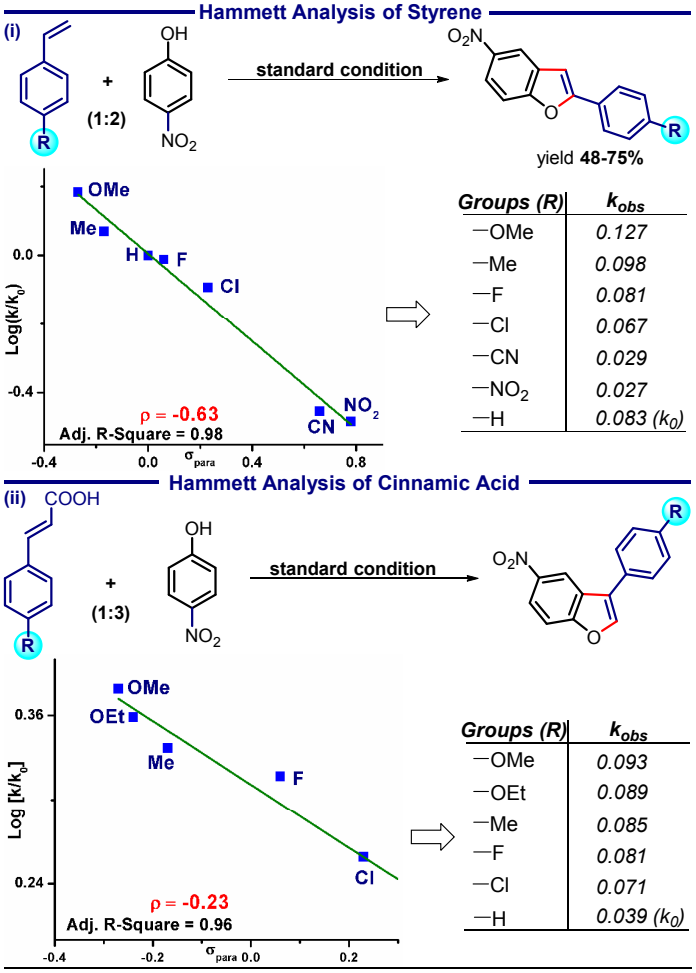
Differential Insertion of Olefin:

Once the palladium phenol is formed, it reacts with the olefinic partner forming the **5** or **6**, the key intermediate to harness regioselective product formation. Hammett analysis on the phenol system, with a series of diverse substituents, suggests the formation of negative charge density. The reaction with electron withdrawing groups are found to be more facile as it favors the stabilizing the negative charge density and palladation (Scheme 4i). A similar substituent effect is observed for 3-substituted benzofuran synthesis (Scheme 4ii).



Scheme 4. Hammett analysis for the reaction of phenol with (i) styrene (ii) cinnamic acid

Hammett analysis on the olefinic partner suggests the formation of partial positive charge density on the system (Scheme 5), which is stabilized by the presence of electron donating groups. However, unlike the styrenyl systems, electron deficient cinnamic acids are consumed without the formation of 3-substituted benzofurans.[85] Such an observation can be rationalized by the facile decarboxylation of electron deficient cinnamic acids prior to the binding of Pd besides its reduced metal binding ability.[87-89]



Scheme 5. Hammett analysis for the reaction of (i) styrene (ii) cinnamic acid

Although both the olefinic partners show the signature of the partial positive charge accumulation, yet the distribution of charge cannot be concluded from the Hammett analysis.

The relative distribution of the computed positive charge on the olefinic carbons (C1 and C2; Figure 2) is found to be different for styrene and cinnamic acid. Relatively more positive charge on the C2 carbon in the case of styrene and that on C1 carbon of cinnamic acid seem more likely. Difference in polarization of the olefinic moiety can result in different migratory insertion and regioselectivity. Notably, a greater slope in Hammett plot for styrene over cinnamic acid aligns with proposed partial positive charge formation at C1 for styrene and C2 for cinnamic acid.

In particular, the DFT calculations[90] on the regio-controlling migratory insertion step provided valuable insights. Different possibilities of the regio-controlling transition states for both styrene (**S**) and cinnamic acid (**CA**) are considered.[85] The calculations suggest that the transition state (TS) for the nucleophilic addition at C2 carbon of styrene ($\mathbf{S_{C2}}$) is 2.2 kcal/mol lower than the addition at C1 ($\mathbf{S_{C1}}$) as shown in Figure 2. On the other hand, the TS for the nucleophilic addition at C1 carbon of cinnamic acid ($\mathbf{CA_{C1}}$) is 5.7 kcal/mol lower than the addition at C2 carbon ($\mathbf{CA_{C2}}$).

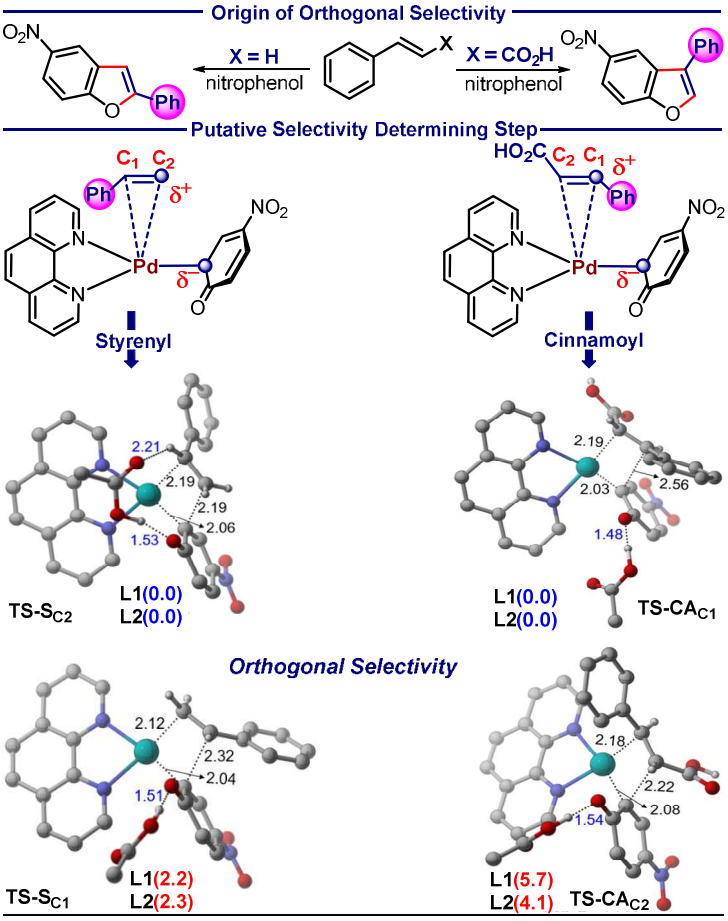


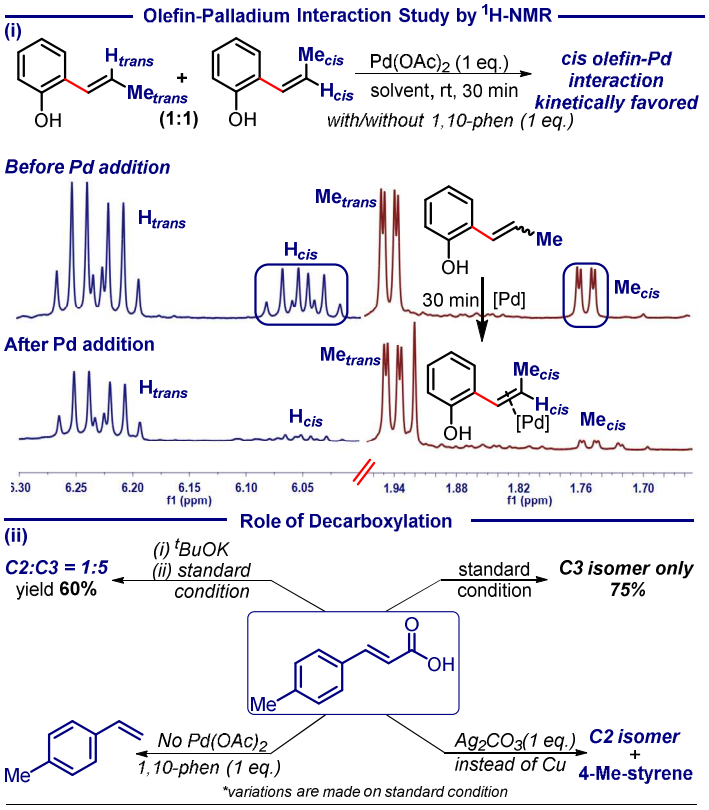
Figure 2. Olefin binding to *ortho*-palladated phenol and optimized TS geometries of the migratory insertion step, **TS(4-5)**. $\Delta\Delta G^{\ddagger}$ (kcal/mol) are in parenthesis. L1=$SMD_{(DCE)}$/B3LYP-D3/def2-TZVP//B3LYP/6-31G**,LanL2DZ(Pd) and L2=$SMD_{(DCE)}$/M06/6-31+G**,SDD(Pd)//B3LYP/6-31G**,LanL2DZ(Pd).

Additional distortion-interaction analysis on these TSs helped us understand the origin of the computed regioselectivity.[49, 91-92] Higher interaction energy between styrene and *ortho*-palladated phenol in $\mathbf{S_{C2}}$ renders C2 addition more favorable in styrene whereas a relatively lower distortion in both the reacting partners (cinnamic acid and *ortho*-palladated phenol) in $\mathbf{CA_{C1}}$ favors addition at C1 carbon in the case of cinnamic acid. [85] In the case of styrene, the difference in Gibbs free energy between the regiocontrolling TSs is found to arise due to higher

interaction energies in the most favored TS geometry that corresponds to the major isomer. However, in the case of cinnamic acid, the distortion energy in the TS leading to the major product is lower, suggesting a prominent role of distortion in regioselectivity (Figure 2).

Impact of Decarboxylation:

Although it is evident that distinct relative charge distribution on olefin is the key to differential regioselective insertion, the decarboxylation of cinnamic acid plays a crucial role to maintain such orthogonality. While studying the interaction of the *ortho*-olefinated phenol (Scheme 6i) with palladium *cis* olefin from a *cis-trans* mixture of 2-propenyl phenol is found to be consumed faster than the *trans* isomer. The interaction of olefinated phenol with palladium can also be observed based on the change of the UV-Vis signal of substrate.[85] Analogous experiments on cinnamic acid revealed that the decarboxylation is a critical step. 4-methyl cinnamic acid when converted to cinnamate and treated under the standard condition, a mixture of 2- and 3-substituted benzofuran is obtained unlike the parent cinnamic acid that exclusively gave 3-substituted benzofuran (Scheme 6ii). In addition, efficient decarboxylation triggers the formation of styrene and 2-substituted product from cinnamic acid.[85] Presumably, moderate decarboxylation rate with catalytic Cu-phen system over other decarboxylative condition reinforced the necessary step sequence. Positioning of decarboxylation following the olefination step is the key requirement for the selectivity. Retaining such step sequence ensured the complementary behavior of olefin and α, β-unsaturated acids.[82, 93-95]

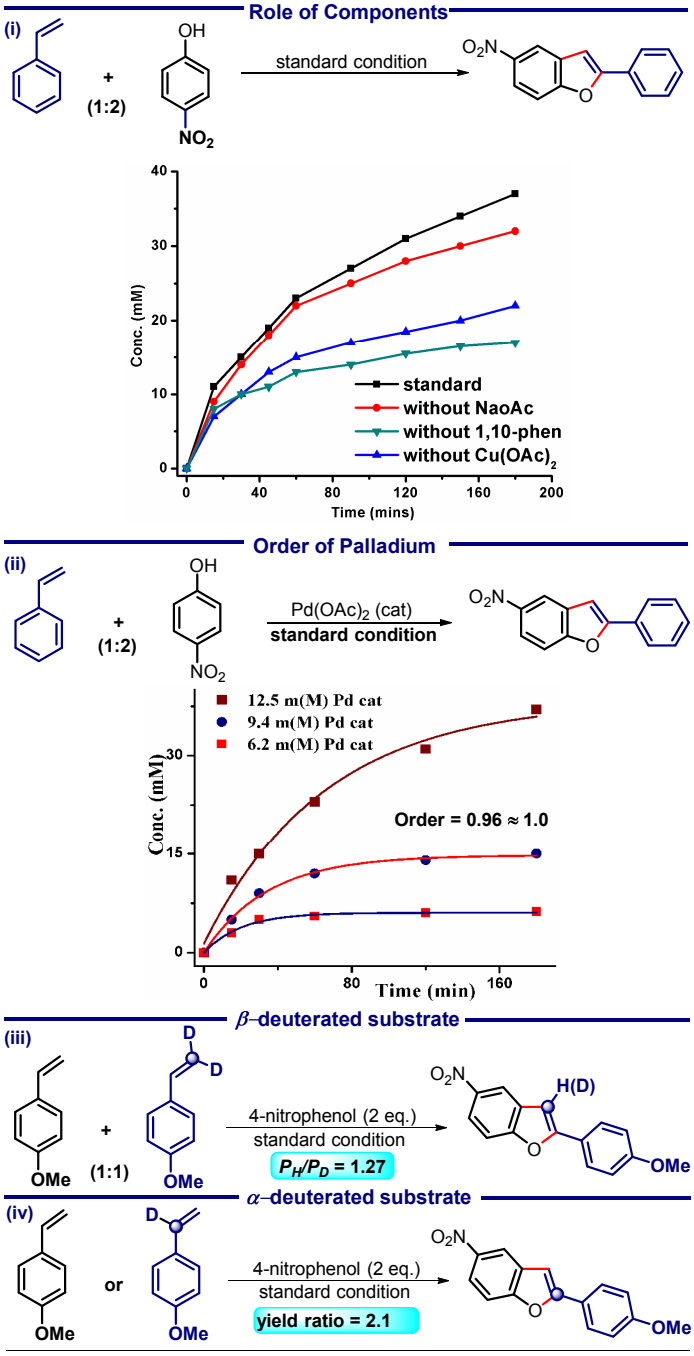


Scheme 6. (i) NMR study of olefin-Pd interaction (ii) Role of Decarboxylation

Kinetics of the reaction:

During the kinetic analysis, unlike styrene, all other components are found to influence the overall yield of the reaction, but not the regioselectivity (Scheme 7i).[85] A similar outcome is also observed for cinnamic acid. Kinetically, a first order rate dependency is noted for palladium under both the conditions (Scheme 7ii).[27] The reaction followed a first order kinetics with phenol and a negative order kinetics with styrene.[23] Isotope labeling experiment with d_2(C2)-4-methoxystyrene shows a product partitioning of 1.27 (P_H/P_D) whereas 4-methoxystyrene is found to be more reactive than d_1(C1)-4-methoxystyrene [P_H/P_D = 2.1]. A value of 1.84 (k_H/k_D) was observed for the o*rtho* C–H bond cleavage of phenol.[23] Such an observation eliminates the possibility of olefinic and *ortho* C–H bond cleavage in the rate determining step (RDS).[96] It is

likely that a steady state equilibrium is maintained among the intermediates with no distinct rate limiting step.[85]



Scheme 7. (i) Role of different components (ii) determination of order, and KIE studies with deuterated olefins (iii) and (iv).

CONCLUSIONS:

We have rationalized how the choice of olefinic coupling partner dictates the regioselective synthesis of 2- and 3-substituted benzofurans starting from a simple phenol precursor. The change in the fashion of olefin insertion upon moving from styrenyl to cinnamoyl system is largely responsible for the regioiselectivity. Although both the olefins develop a partial positive charge during the course of the reaction, their relative distributions are different and thus the mode of migration. Such distinctions are maintained only when insertion of cinnamoyl group occurs prior to decarboxylation. A change in such step sequence leads to the loss of regioselectivity. Thus, under a facile decarboxylative condition orthogonal behaviour is compromised and both the olefins lead to similar regioisomeric products. Therefore, maintaining migratory insertion followed by decarboxylation step is the key requirement for an olefin dependent regioselective synthesis of benzofurans.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest

Supporting Information

All the experimental details, procedures, spectroscopic characterizations, crystallographic data (CIF) are provided in the supporting information.

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TOC Graphic: