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Ambiphilic Reactivity of Vinyl Pd Oxyallyl for Expeditious Construction of Highly Functionalized Cyclooctanoids

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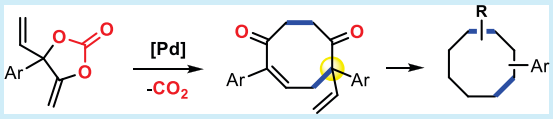
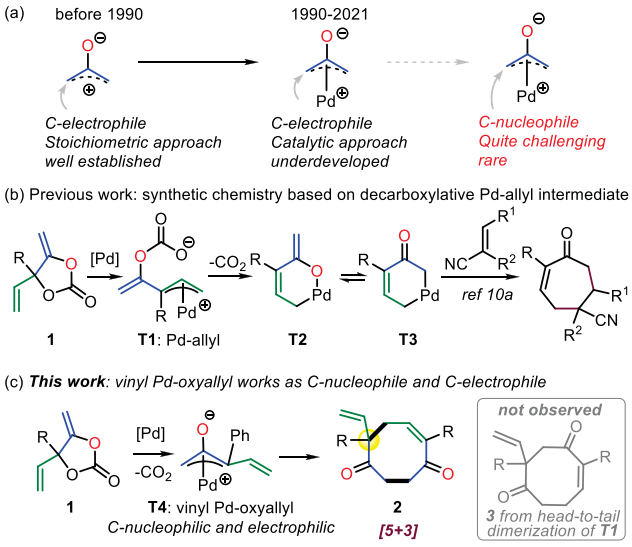
ABSTRACT: We report the catalytic generation of a vinyl Pd-oxyallyl that dimerizes regiospeci cally to form highly functionalized nonbridged cyclooctanoids. Such compounds are otherwise synthetically challenging, but highly useful in synthesis. This vinyl Pd-oxyallyl species demonstrates both electrophilic and nucleophilic properties. DFT calculations elucidate the mechanism and the origins of the chemoselective cyclooctanoid formation.



Cycloaddition reactions are invaluable tools for the construction of interesting and important molecules in synthetic chemistry.[1] The development of novel strategies for cycloadditions is largely dependent on the design of new substrates that can give reactive cycloaddends for subsequent controllable annulations with suitable acceptors.

Oxyallyl cations, although highly reactive and unstable by nature, have attracted much research interest mainly due to their diverse and ambiphilic characteristics.[2] Traditionally, oxyallyl cations are produced from -substituted ketones or enol ethers in the presence of stoichiometric additives,[2,3] or from the oxidation of allenamides.[4] In contrast, catalytic generation and cycloaddition of oxyallyl cations has been much less investigated despite the fact its synthetic potential has been unveiled as early as the 1990s.[5] Recent work by Trost and co-workers,[6] in combination with calculations by the Houk group,[7] uncovered intermolecular (3 + 2) annulations between Pd-oxyallyl species and electron-rich dienes; this pioneering work demonstrated that the reactivities of the Pd-oxyallyl intermediate vary with substituents;[6,7] the use of appropriate ligands also proved to be crucial for efficient reactions in this Pd-based catalytic system. The Zi group recently reported an intriguing synthesis of carbocycles via the intermediacy of Pd-oxyallyls featuring an electron-withdrawing group in the presence of a Lewis acid.[8] Though synthetically capable, oxyallyl intermediates typically exhibit electrophilic properties in cycloadditions, and favor the electron-rich alkenes or dienes as partners (Scheme 1a).[5 8] This greatly limits their application in synthesis. Accordingly, the exploration of nucleophilic reactivities of Pd-oxyallyl species is quite challenging (Scheme 1a). As the counterpart of Pd-oxyallyls, Pd-allyl intermediates have been powerful components in cycloadditions in the past two decades.[9] We envisaged that the presence of a vinyl group would influence the electronical property of the Pd-oxyallyl intermediates and might provide opportunities for solving otherwise synthetically challenging cycloadditions. The vinyl Pd-oxyallyl exhibits potential as 1,3

Scheme 1. a) Advances of Oxyallyl Chemistry; b-c) Pd-Catalyzed Decarboxylative Chemistry of Vinyl Methylene Carbonate: Pd-Allyl vs Pd-Oxyallyl Intermediates



C C, 1,3 O C, 1,5 O C, or 1,5 C C zwitterionic building blocks. Our laboratory[10a d] and the Zi group[10e] independently designed and synthesized a vinyl methylene carbonate **1**, a potential precursor of intermediates **T1** **T4** on the basis of Pd-allyl or Pd-oxyallyl chemistry upon decarboxylation with

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palladium catalysis (Scheme 1b and c). Previous results suggested that the capture of intermediates **T1** **T3** derived from Pd-allyl chemistry with activated alkenes or amines, enabling the construction of cycloheptenones,[10a] cyclopentanones,[10a e] and N/O-heterocycles.[10b d] However, the catalytic generation and identi cation of vinyl Pd-oxyallyl **T4** is elusive and has never been realized mainly due to the interference of Pd-allyl generation.[10] We now report the catalytic generation, identi cation, and reaction of vinyl Pd-oxyallyl intermediate **T4**. Interestingly, in contrast with the nucleophilic reactivity of Pd-oxyallyl reported previously,[5 7] this vinyl Pd-oxyallyl **T4** displayed both electrophilic and nucleophilic properties which enabled the rst efficient intermolecular [5 + 3] annulations for the construction of various highly functionalized nonbridged cyclooctanoids.[11] Eight-membered carbocycles are well-known medium-sized rings and are encountered in some bioactive and natural products;[12] their diverse synthesis via intermolecular annulation is often difficult due to the high ring strain, complex conformational properties, and repulsive transannular interactions.[12b] Inspired by the synthetic importance of cyclooctanoids and the unique reactivity of vinyl Pd-oxyallyl, we also explored more thoroughly the origin of this unique reactivity in combination with DFT calculations.

It was found that the use of $Pd(Ph_3P)_4$ as catalyst at 110 °C in mesitylene is the most productive (see Supporting Information (SI) for the optimizations). This protocol is quite efficient for various substrates under the optimized conditions, and gives cyclooctanoids with carbonates substituted by both electron-withdrawing (**2a** **2g**, **2o** **2q**, and **2s**) and -donating (**2h** **2k** and **2t**) aryl groups (Figure 1). The structure of the product **2m** was unambiguously con rmed by single crystalline X-ray analysis (inset of Figure 1).[13] The OCF_3-containing compounds showed attractive lipophilic and electronic properties and have found important applications in pharmaceutical development.[14] The current procedure offered an alternative pathway for the synthesis of product **2g** bearing an OCF_3 group. The successful introduction of bromo- and boryl-functional groups (**2b**, **2l**, and **2o**) would facilitate further utilization of the corresponding products in Suzuki and Heck coupling reactions. The installation of a bulky naphthyl group proved to be feasible, with the formation of a 63 yield of the corresponding product (**2t**). This catalytic system was applicable for those substrates featuring both *para*- (**2a** **2l**, **2q**) and *meta*-substituted (**2n** **2q**) aryl groups, but showed some limitations for the conversion of the carbonates with *ortho*- functionalized aryl substituents. For instance, the *ortho*-F-Ph substituted carbonates (**1s**) showed much better activities than the *ortho*-Br-Ph substituted ones, suggesting the larger bromide might be exhibiting an unfavorable steric effect. The two carbonyl groups equipped in products **2a** **2t** facilitate their further derivatizations in synthesis which adds further to the attractiveness of this methodology. Attempts to achieve the cross-coupling between two electronically different carbonates **1c** and **1h** under the optimized conditions led to a complex reaction mixture.[15] Compounds **2a** **2t** contain quaternary carbon centers, which are challenging to build otherwise in synthesis.[16] Note that the carbonate with better electron-donating group (**1i** or **1t**) is relatively less stable, and some cyclopentenones derived from Nazarov-type reactions (**4i** and **4t**, Figure 1) could be observed when standing in the air for some time; this type of transformation has been previously detailed by Yamada and co-workers.[17] Speci cally, the furan-substituted carbonate **1u** was converted *in situ* into

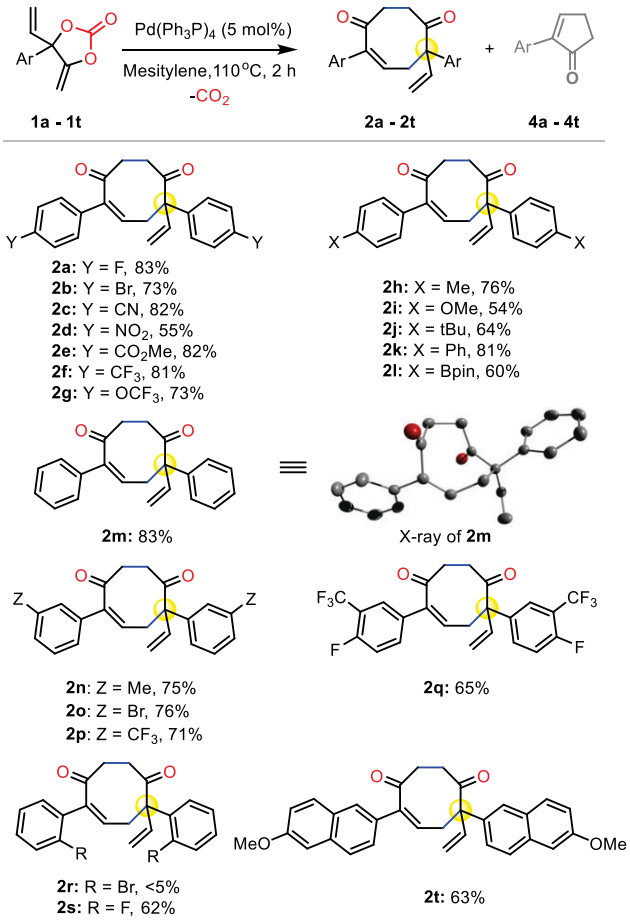

Figure 1. Carbonate scope in the formation of cyclooctanoids **2a** **2t**. The inset is the solid state of product **2m** and the hydrogen atoms are omitted for clarity at 50 probability for the drawing of thermal ellipsoids.

the cyclopentenone **4u** during the carbonate synthesis stage (Figure 2).[17] The introduction of an extra phenyl (**1v**) or methyl (**1w**) group on the vinyl group of the carbonate is feasible, although ketone products (**4v** or **4w**) were isolated

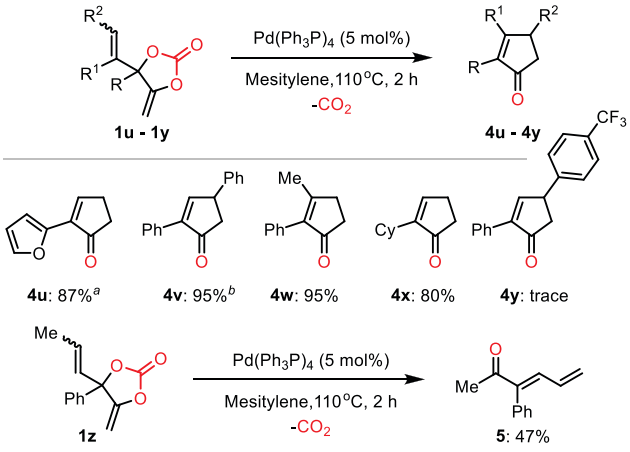

Figure 2. Formation of ve-membered ketones **4u** **4y** and diene **5** with carbonates **1u** **1z** as substrates. [a]In situ formed from the alcohol during the preparation of carbonate **1u**. [b]About 20 of ketone **4v** observed during the preparation of carbonate **1v**.

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quantitatively under the optimized conditions similar to the performance of cyclohexyl-substituted substrate **1x** (Figure 2). In contrast, the use of CF_3-substituted carbonate **1y** gave rise to a complex reaction mixture, although it is much more stable compared to carbonate **1v**; this indicates an electronic effect on the stability and reactivity of the carbonate substrate. The formation of a diene product **5** was observed when carbonate **1z** was used for the reaction probably due to the β-elimination of the palladium intermediate **A** (see Figure 2 and Scheme 1). These results (Figures 1 and 2) further demonstrated that the generation and reactivities of oxyallyl cations/Pd-oxyallyl hinge heavily on its substituents, as observed and calculated by others.[2a,6,7]

The synthetic potential of the cyclooctanoid products was demonstrated by the derivatization of **2m** under different reaction conditions (Figure 3).[18] Note that compound **2m**

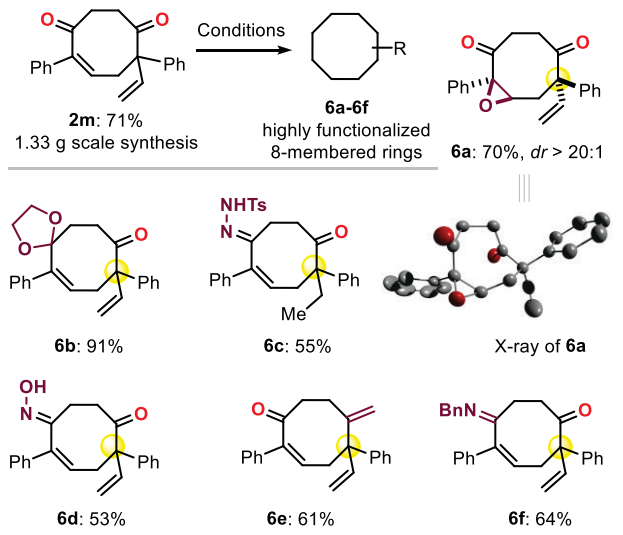

Figure 3. Synthetic transformations of product **2m** into highly functionalized eight-membered cyclic structures. **6a**: *p*-TsOH·H_2O (10 mol), *m*-CPBA (2.5 equiv), benzene, rt, 24 h; **6b**: 2-ethyl-2-methyl-1,3-dioxolane (20 equiv), ethylene glycol (0.6 equiv), BF_3·Et_2O (3.0 equiv), anhydrous $CHCl_3$, N_2, rt, 120 h; **6c**: $TsNHNH_2$ (5 equiv), 4Å molecular sieves, anhydrous CH_3OH, 60 °C, N_2, 10 h; **6d**: NH_2OH·HCl (1 equiv), Pyridine, 60 °C, N_2, 12 h; **6e**: methyltriphenyl-phosphonium bromide (2 equiv), *n*-BuLi (2 equiv), anhydrous (benzene/THF 1/1), 80 °C, N_2, 4 h; **6f**: $BnNH_2$ (5 equiv), glacial acetic acid (5 equiv), 4 Å molecular sieves, anhydrous CH_3OH, 50 °C, N_2, 4 h. See the SI for details. Inset is the solid state of epoxide **6a** and the hydrogen atoms are omitted for clarity at 50 probability for the drawing of thermal ellipsoids.

could be prepared in a gram scale (1.33 g, 71). Selective oxidation gave rise to epoxide **6a** with the vinyl group unaffected. The molecular structure is further characterized with X-ray analysis (inset in Figure 3). One of the carbonyl groups could be converted into spiroketal **6b**. The successful syntheses of the corresponding hydrazone **6c** or oxime **6d** may bring new opportunities for pharmaceutical development. The Wittig reaction allowed the installation of an extra double bond on the cyclooctanoid skeleton (**6e**). An eight-membered imine product **6f** could be obtained in good yield when reacted with benzyl amine under anhydrous conditions. All these transformations suggested that the products **2a** **2t** obtained in this catalytic system would give a fast access toward highly functionalized and otherwise synthetically challenging medium-sized cyclic structures.

To determine the reaction mechanism and origins of chemoselectivity observed with carbonates **1a** **1t** as substrates, we explored the reaction mechanism with density functional theory. The computational method was B3LYP-D3(BJ)/def2-TZVP, SMD mesitylene (eps = 2.4, epsinf = 2.247) energies computed on B3LYP-D3(BJ)/def2-SVP geometries.[19] We were particularly interested in understanding the chemoselectivity in this system toward the formation of product **2** rather than **3**. In the presence of $Pd(PPh_3)_4$, decarboxylation of the substrate occurs leading to intermediate **t1**. Zi et al. proposed a six-membered structure of the vinyloxallyl cation Pd complex.[10e] We explored this structure and that of a Pd-oxallyl complex, and found that **t1** is lower in energy by 8.0 kcal/mol (Figure S1 in SI). We assume, therefore, that **t1** is the effective intermediate in this reaction. Starting from **t1**, we explored the Gibbs free energy surfaces for the formation of cyclooctanoid **2m**. The results are summarized in Figure 4a, while some of the important optimized structures are shown in Figure 4b. The intermediate **t1** formed upon decarboxylation features η^2 Pd-coordination to the oxyallyl cation and has a somewhat unsymmetrical structure with Pd C bond lengths of 2.2 2.4 Å. The displacement of one triphenylphosphine ligand from **t1** and reaction with another molecule of carbonate leads to the formation of **t2** with release of CO_2. The coupling of the two vinyl oxyallyl ligands in **t2** gives **t3** via a low-energy transition state **TS1** with an energy barrier of only 25.7 kcal/mol (*path a*). The isomeric coupling of **t2** (*path b*) would lead to the formation of isomeric cyclooctanoid **3m** via a transition state of **TS1** , but this process has a very high barrier of 37.1 kcal/mol. While the calculated structures appear similar, note that **TS1** requires the highly favorable Pd-oxyallyl bonding to be replaced by less favorable Pd-vinyl binding which is substantially higher in energy (Figure 4b). The intermediate **t3** involves a structure similar (Figure S2 in SI) to that of **TS1** but with the Pd binding only to two adjacent carbons of each fragment; the Pd rearranges spontaneously to bridge the allyl group (Figure 4a, **t3** **t4**). The intermolecular nucleophilic attack of **t4** leads to the formation of the Pd-bonded product **2m** via transition state **TS2** with an energy barrier of only 6.5 kcal/mol. These results suggested that the C C coupling is probably the rate-determining step. In order to better understand why *path b* through **TS1** has higher energy than the *path a* via **TS1** (Figure 4a), and why the Pd favors the coordination with the oxyallyl fragment in **t1** rather than the vinyl group in this catalytic system, we explored the frontier molecular orbitals (FMOs) of the vinyl-oxyallyl moiety in **t1** (Figure S3 in SI). It is clear that both the HOMO and LUMO of the vinyl-oxyallyl moiety are localized on the oxyallyl fragment which provides stronger coordination to the Pd(II). The intermediate **t2** (Figure 4) is ideally set up for the formation of a new C C bond between the two oxyallyl fragments resulting in **t3** with a ligand reorganization process around the Pd atom.

In conclusion, we have described the catalytic generation and identi cation of vinyl Pd-oxyallyl intermediate exhibiting unique reactivity. Compared with the reactivity of Pd-oxyallyl intermediate reported previously, this vinyl Pd-oxyallyl species showed both electrophilic and nucleophilic properties which enabled the rst efficient but challenging intermolecular [5 + 3] annulations for the construction of various highly functionalized nonbridged cyclooctanoids. DFT calculations

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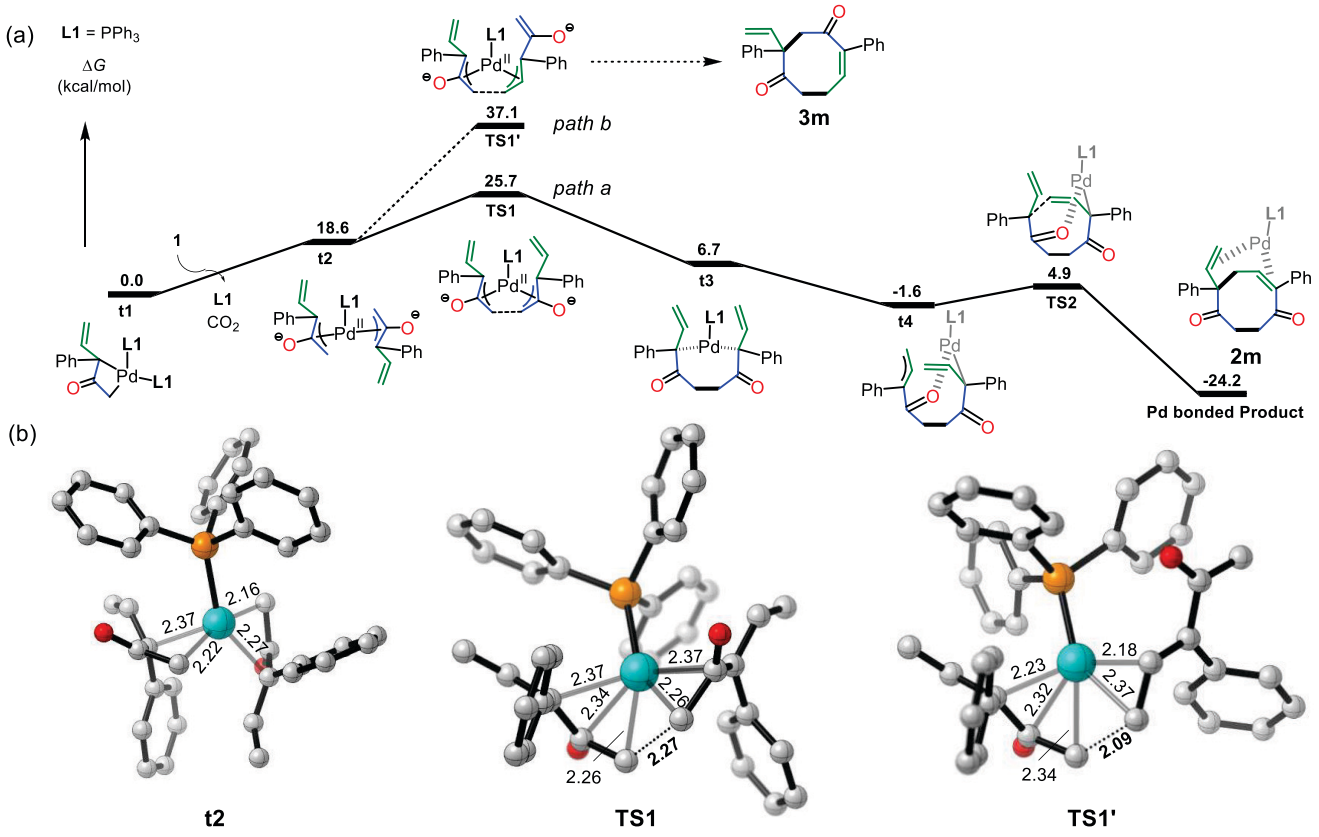

Figure 4. (a) DFT-computed energy pro le for the formation of cyclooctanoids **2** and **3** and (b) the calculated structures of transition states **TS1** and **TS1** , and intermediate **t2**. All the hydrogen atoms are omitted for clarity; selected bond distances are labeled in Å.

explain the chemoselective formation of the corresponding cyclooctanoid products. These ndings broaden the scope of catalytic reactions based on the use of Pd-oxyallyl species as carbon nucleophiles. The exploration of the reactivity of these carbonate substrates is ongoing in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02401.

Experimental details and characterization data (PDF)

Accession Codes

CCDC 1950691 1950692 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

‖L.Z. and P.M. contributed equally.

Notes

The authors declare no competing nancial interest.

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(18) See CCDC-1950692 for X-ray analysis results of **6a**.

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