A Domino Process towards Functionally Dense Quaternary Carbons through Pd-Catalyzed Decarboxylative Csp^3-Csp^3 Bond Formation

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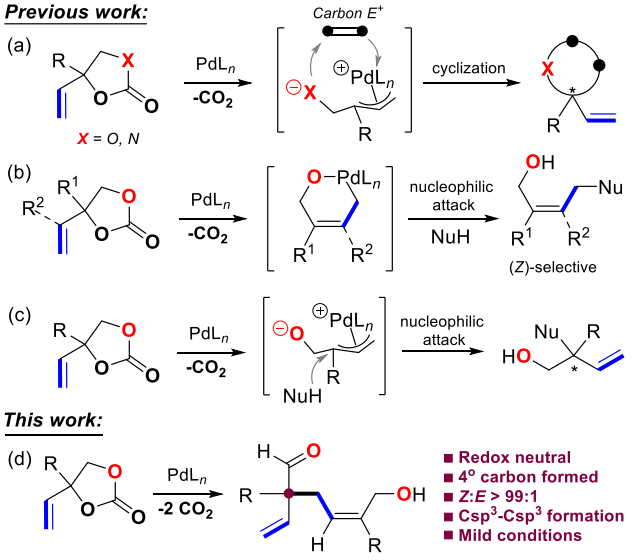
ABSTRACT: An efficient protocol was developed to construct functionally dense quaternary carbons with concomitant formation of a new Csp^3-Csp^3 bond via Pd-catalyzed decarboxylative transformation of vinyl cyclic carbonates. This redox neutral catalytic system features stereocontrolled formation of multi-substituted allylic scaffolds with an aldehyde functionality generated in situ, and it typically can be performed at room temperature without any additives. DFT calculations provide a rationale towards the selective formation of these compounds, and revealed a complex mechanism that is able to reproduce with the help of microkinetic models the non-trivial dependence between the identity of the product and the nature of the substituents in the substrate.

INTRODUCTION

For synthetic chemists, the ultimate goal is to synthesize highly functionalized building blocks in a single step under mild reaction conditions generating minimal waste. Transition metal catalyzed decarboxylative processes have emerged as attractive and powerful methodologies in synthetic chemistry generating only CO_2 as a byproduct and gained extensive interest.[1] Quaternary (chiral) carbons are ubiquitous in natural products and pharmaceutically relevant compounds albeit the construction of highly functionalized quaternary (chiral) carbons represents a challenging task.[2] Decarboxylative construction of quaternary carbons has been realized in an intramolecular fashion,[3] whereas the intermolecular coupling of reaction partners generating highly functionalized quaternary carbons with new Csp^3-Csp^3 bond formation via decarboxylative methodologies under mild conditions is still in its infancy.[1,4]

Previous work demonstrated that the Pd-catalyzed decarboxylative construction of quaternary carbon centers is feasible via the reaction of an external electrophile with a vinyl cyclic carbonate/carbamate under mild reaction conditions (Scheme 1a).[5–7] The key to success of these transformations is the *in situ* formation of a zwitterionic π-allyl-Pd intermediate upon CO_2 extrusion.[5-7] As part of our ongoing research work on the transformations of cyclic carbonates,[8] we developed a conceptually novel approach involving the use of nucleophiles toward the synthesis of (*Z*)-stereoselective allylic manifolds through a judicious choice of the catalyst source and ligand.[9] The mechanistic rationale based on DFT calculations[9a] suggested that a six-membered palladacycle intermediate is crucial to control the stereoselectivity of the process (Scheme 1b). More recently, the enantioselective synthesis of branched allylic amines, alcohols or ethers with tertiary carbons was also achieved using vinyl cyclic carbonate precursors (Scheme 1c).[10] Interestingly, during the course of our studies[9a] we frequently encountered trace amounts (< 3%) of an aldehyde byproduct in the reaction mixture based on NMR analysis. Considering the synthetic importance of aldehydes,[11] efforts were made to reveal the molecular identity of this byproduct. The rather unexpected and multifaceted nature of this product suggested that the coupling of two molecules of vinyl cyclic carbonate had occurred upon extrusion of two CO_2 molecular (Scheme 1d). The formation of this aldehyde product features the construction of an otherwise synthetically challenging quaternary carbon center and a stereodefined, multi-substituted allylic alcohol fragment. Taking into account the synthetic application potential of this aldehyde product (Scheme 1d),[11] we set out to examine the generality of this chemistry and to gain detailed insight for this unusual coupling process.[12]

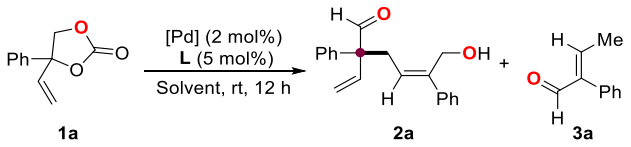
Scheme 1. Pd-Catalyzed Decarboxylative Transformations of Vinyl Cyclic Carbonate/Carbamate



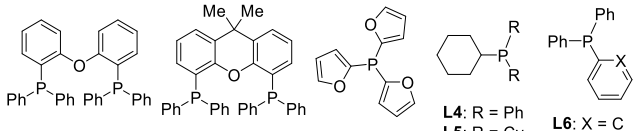
RESULTS AND DISCUSSION

We selected the phenyl-substituted cyclic carbonate **1a** as a model substrate for the optimization of the reaction conditions (Table 1). To our delight, the utilization of $[Pd_2(dba)_3]\cdot CHCl_3$ and DPEPhos (**L1**) in DMF under anhydrous conditions at room temperature gave rise to an appreciable yield (66%) of the targeted aldehyde product **2a** with concomitant formation of the substituted acrolein byproduct **3a** (entry 1).[13] In the presence of **L1**, the use of the White catalyst precursor afforded the highest yield (85%) of product **2a** (Table 1, entry 1–5) although the use of $Pd(dba)_2$ led to a higher ratio of **2a**:**3a** (Table 1, entries 2 *vs* 5). The use of other solvents such as THF, DCM and acetonitrile (ACN) under anhydrous conditions resulted in less efficient catalysis (Table 1, entries 6–8). Importantly, poor reactivity was observed in the presence of other ligands (**L2–L7**) or under ligand-free conditions indicating the crucial role of ligand **L1** towards the success of this transformation (entries 9–15).

Table 1. Optimization of the Reaction Conditions towards the Formation of Aldehyde Product 2a.[a]



Entry	Catalyst	L	Solvent [1 M]	Yield **2a**[%]	**2a**:**3a**
1	$[Pd_2(dba)_3]\cdot CHCl_3$	**L1**	DMF	66	70:30
2	$Pd(dba)_2$	**L1**	DMF	77	93:7
3	$Pd(OAc)_2$	**L1**	DMF	77	80:20
4	$(PPh_3)_2PdCl_2$	**L1**	DMF	<10	90:10
5	Pd/bis-sulfoxide	**L1**	DMF	85	90:10
6	Pd/bis-sulfoxide	**L1**	THF	61	84:16
7	Pd/bis-sulfoxide	**L1**	ACN	26	80:20
8	Pd/bis-sulfoxide	**L1**	DCM	81	86:14
9	Pd/bis-sulfoxide	**L2**	DMF	0	-
10	Pd/bis-sulfoxide	**L3**	DMF	<5	-
11	Pd/bis-sulfoxide	**L4**	DMF	0	-
12	Pd/bis-sulfoxide	**L5**	DMF	0	-
13	Pd/bis-sulfoxide	**L6**	DMF	0	-
14	Pd/bis-sulfoxide	**L7**	DMF	0	-
15	Pd/bis-sulfoxide	-	DMF	0	-



[a]Reaction conditions: 0.20 mmol of carbonate, 0.20 mL of solvent, rt, anhydrous conditions, under N_2; Pd/bis-sulfoxide refers to White catalyst, ACN = acetonitrile. The yield and ratio of **2a**:**3a** were determined by ^1H NMR ($CDCl_3$) using toluene as internal standard.

With the optimized reaction conditions in hand (Table 1, entry 5), a series of vinyl cyclic carbonates (**1a-r**) was then investigated toward the synthesis of a wider array of highly functionalized aldehyde products (*cf.*, formation of **2a-r**, Figure 1). The

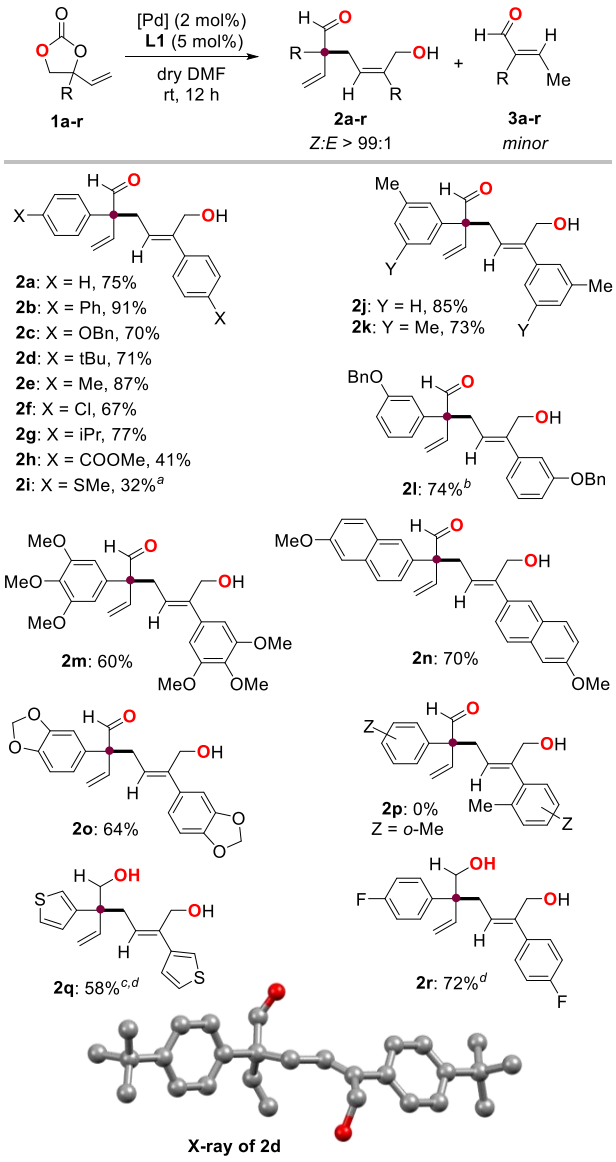


Figure 1. Scope of carbonates toward the formation of aldehyde products **2a-r**. Reaction conditions unless stated otherwise: 0.2 mmol carbonate, White catalyst (2.0 mol%) and **L1** (5.0 mol%) in anhydrous DMF (0.20 mL), rt, under N_2, 12 h. [a] 80 °C, 10 mol% of the White catalyst, 20 mol% **L1**. [b]18% of **3l** was isolated and fully characterized, see supporting information (SI) for details. [c]5.0 mol% of the White catalyst and 10 mol% **L1** used. [d]Yield of the corresponding reduced diol product upon treatment with $NaBH_4$.

developed catalytic system tolerated a range of electron-donating (**2d-e, 2g** and **2j-2o**) and -withdrawing (**2f**, **2h** and **2r**) functionalities present in the aryl substituent of the carbonate substrate. The introduction of thioether and thiophene functionalities was also feasible as exemplified by the syntheses of products **2i** and **2q** though higher reaction temperatures and/or higher catalyst loading were required.[14] The installation of substituents on the *meta*-position of the aryl group (R) of the carbonate substrate did not affect the efficiency of the catalytic process and products **2j-m** and **2o** could be isolated in good yields. The attempted synthesis of product **2p** from the *o*-methyl-aryl substituted carbonate failed and no reaction was observed, not even with an increased catalyst loading (10%) at el-

evated reaction temperature (80°C). In this latter case, quantitative recovery of the starting carbonate was noted, thus indicating some steric limitations of this protocol. The formation of the aldehyde **2o** containing a 1,3-benzodioxole fragment is of relevance for pharmaceutical development programs.[15] Considering the generally reactive nature of aldehydes, the synthesis of highly functionalized compounds such as **2a-r** would be rather challenging using sensitive metal reagents.[16]

No reaction was observed in the presence of a phosphoramidite type ligand in an attempt to prepare compound **2a** enantioselectively further confirming the privileged role of ligand **L1** (see also Table 1, entries 9–14).[17] It should be noted that during the synthesis of aldehyde products **2a-r** virtually no (*E*)-configured products were formed. This feature adds further to the attractiveness of this decarboxylative protocol as stereoselective synthesis of highly substituted alkenes is a challenging task.[18] It is worth noting that products **2a-r** also represent highly functionalized allylic alcohols which are important building blocks and intermediates in synthetic chemistry.[19] The (*Z*)-configuration of all the products was supported by 2D ^{1}H-^{1}H NOESY NMR spectra analysis (see SI for details), and was further unambiguously confirmed by the X-ray analysis of aldehyde product **2d** (bottom inset in Figure 1).[20] With the attempt to achieve the cross-coupling between two different vinyl cyclic carbonates, carbonates **1a** (0.1 mmol) and **1b** (0.1 mmol) were mixed under the optimized conditions. Unfortunately, a complex product mixture was obtained containing at least four different aldehyde products based on the ^{1}H NMR analysis of the reaction crude mixture. Similar observations were done when carbonates **1a** and **1i** were reacted under comparable conditions (see SI for details).[21]

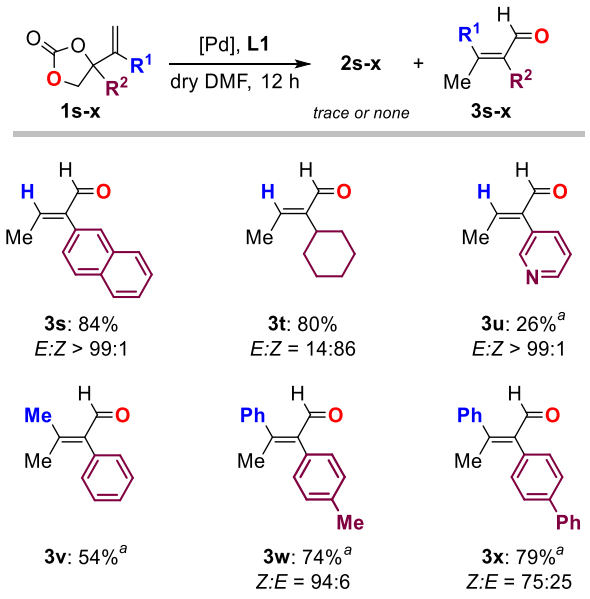


Figure 2. Scope of carbonates toward the formation of aldehyde products **3s-x**. Reaction conditions unless stated otherwise: 0.20 mmol carbonate, White catalyst (2.0 mol%) and **L1** (5.0 mol%) in anhydrous DMF (0.20 mL), rt, under N_2, 12 h; no or traces of aldehydes **2s-x** were observed. [a]5.0 mol% of White catalyst, 10 mol% of **L1** were used, 80°C.

Unlike the reactivity of MeO-naphthyl substituted cyclic carbonate **1n** to afford aldehyde product **2n** (Figure 1), the use of naphthyl-substituted carbonate **1s** afforded as major product the aldehyde **3s** (**2s**:**3s** = 7:93 based on ^{1}H NMR) in 84% isolated yield (Figure 2) suggesting the significant electronic effect in this transformation. The utilization of alkyl-substituted carbonate **1t** and several more challenging carbonates **1u-x** (having heteroatoms or disubstituted double bonds) also gave rise to aldehydes **3t-x** as major products. Mostly trace amounts of aldehyde products **2t-x** were noted further illustrating the electronic and steric effects of the carbonate substituents in this decarboxylative catalytic system (Figure 2).

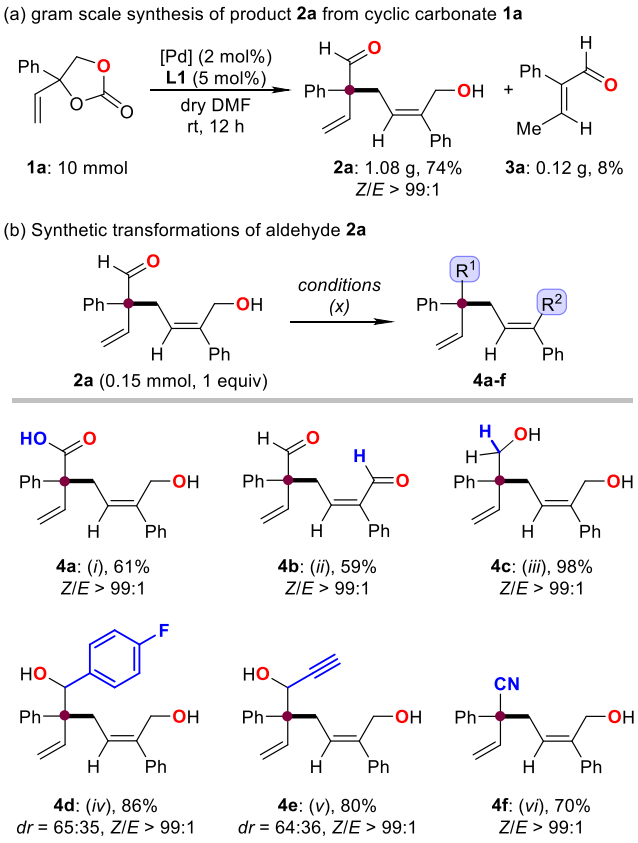
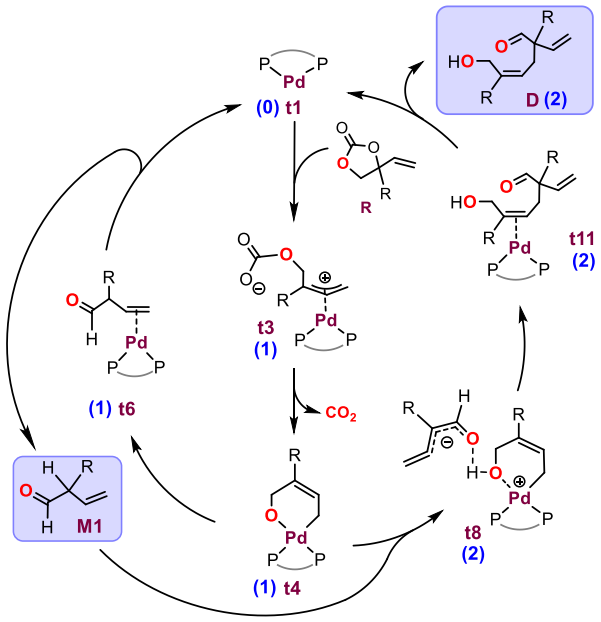


Figure 3. (a) Gram scale synthesis of aldehyde **2a**, and (b) synthetic transformations of **2a** under different reaction conditions: (i) NaH_2PO_4 (0.25 equiv), H_2O_2 (1.1 equiv), $NaClO_2$ (1.4 equiv), ACN/H_2O = 7:3, rt, 12 h; (ii) pyridinium chlorochromate (PCC) (1.5 equiv), silica gel (1.3 equiv), anhydrous DCM, rt, 12 h; (iii) $NaBH_4$ (1.1 equiv), MeOH, 0°C, 3 h; (iv) 4-F-C_6H_4MgBr (3 equiv), THF, 0-rt, 12 h; (v) HC≡CMgBr (3 equiv), THF, –40°C, 10 h; (vi) *O*-(diphenylphosphinyl)-hydroxylamine (DPPH) (1.15 equiv), toluene, rt–85°C, 8 h. See SI for details.

This catalytic system can be easily scaled up as demonstrated by the successful gram scale synthesis of **2a** (Figure 3a). The synthetic potential of the aldehydes **2a-r** was then explored in the synthesis of other highly functionalized scaffolds featuring a quaternary carbon center and a stereo-defined tri-substituted alkene fragment (Figure 3b). For example, the aldehyde group can be selectively oxidized to carboxylic acid **4a** without affecting the vinyl and alcohol groups.[16] Treatment of **2a** with pyridinium chlorochromate (PCC) afforded dialdehyde **4b** in 59% yield. Selective reduction of the aldehyde group with $NaBH_4$

gave access to diol **4c** in nearly quantitative yield (98%). Addition of Grignard reagents to **2a** afforded secondary alcohols **4d** and **4e** in 86% and 80% yield, respectively. The aldehyde group in **2a** was easily transformed to the corresponding nitrile **4f** by treatment with *o*-(diphenylphosphinyl)-hydroxylamine (DPPH).[22] Selective dihydroxylation of the internal alkene fragment also proved to be feasible.[23] All these transformations illustrate the synthetic potential of the highly functional aldehydes obtained through this decarboxylative methodology.

Scheme 2. Simplified Catalytic Cycle for Carbonate 1a Derived from the DFT Calculations. The Blue-Colored Numbers in Parentheses Highlight the Number of Cyclic Carbonate Fragments Included in Each Species



MECHANISTIC INSIGHTS

DFT calculations were performed in order to gain insight into the reaction mechanism. We were in particular interested in understanding the dependence of the reactivity on the nature of the substitution in the carbonate substrate. A series of substrates (Figure 1) produce as major product the aldehyde species **2a-r**, where fragments from two molecules of substrate are integrated into each molecule of product. In contrast, other substrates (Figure 2), produce at most only traces of species **2**, with the major product being aldehyde **3** resulting from a single molecule of vinyl carbonate. For our calculations we used the system comprising of the catalyst derived from the White precursor and DPEPhos (**L1**) and cyclic carbonate substrates **1a** (Figure 1; R = Ph) and **1s** (Figure 2; R^1 = H, R^2 = 2-naphthyl). The reactants differ only in the carbonate substituent yet yield rather different products. The results reported in what follows correspond to geometry optimizations with the B97D functional in DMF solvent followed by single point calculations with a SDD basis set for Pd and 6-311++G(d,p) for all other atoms. All reported energies (in kcal/mol) are free energies in solution.[24] The same method was also used in our previous study concerning the synthesis of allylic amines.[9a]

We will present first and in more detail the results for the catalytic system using carbonate **1a** producing the aldehyde product **2a**. A simplified view of the computed catalytic cycle is shown in Scheme 2, in which substrate **1a** has been labeled as **R** (reactant), and the allylic alcohol product **2a** as **D** (dimer). The initial part of the mechanism is shown in Figure 4. There is an additional aldehyde species different from that observed experimentally that is labeled as **M1**. The species inside the cycle are labeled with the prefix **t**, for theoretical. All the species involved are included in the free energy profiles in Figures 4 and 5 (see also Figures S1-S4 in SI). The reaction starts in a way analogous to the amination process reported previously which is outlined in Scheme 1b.[9a] Substrate **R** first coordinates to the catalyst **t1**, and oxidatively cleaves a C–O bond to reach intermediate **t3** and after extrusion of CO_2 forms the palladacycle intermediate **t4** (Scheme 2 and Figure 4). In the reported amination process,[9a] **t4** received the aniline nucleophilic attack toward the formation of the allylic amine product. The cyclic carbonate is, however, not nucleophilic enough to attack **t4**, and thus other alternative low-energy paths have to be considered.

Intermediate **t4** can rearrange to intermediate **t6**, which can then release aldehyde **M1** through a low-energy barrier recovering the catalyst **t1** (Scheme 2). The formation of **M1** is exergonic, though not enough to be a final product.[25] However, aldehyde **M1** is sufficiently nucleophilic to attack **t4**, and Figure 5 shows the continuation of this reaction.

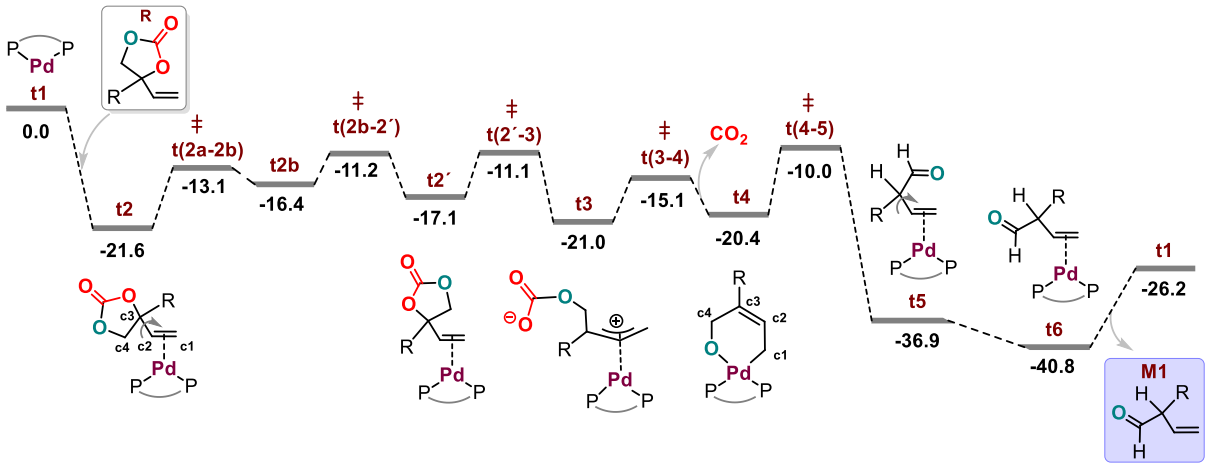


Figure 4. Free energy profile (in kcal/mol) for the first part of the catalytic cycle leading to the departure of aldehyde **M1**.

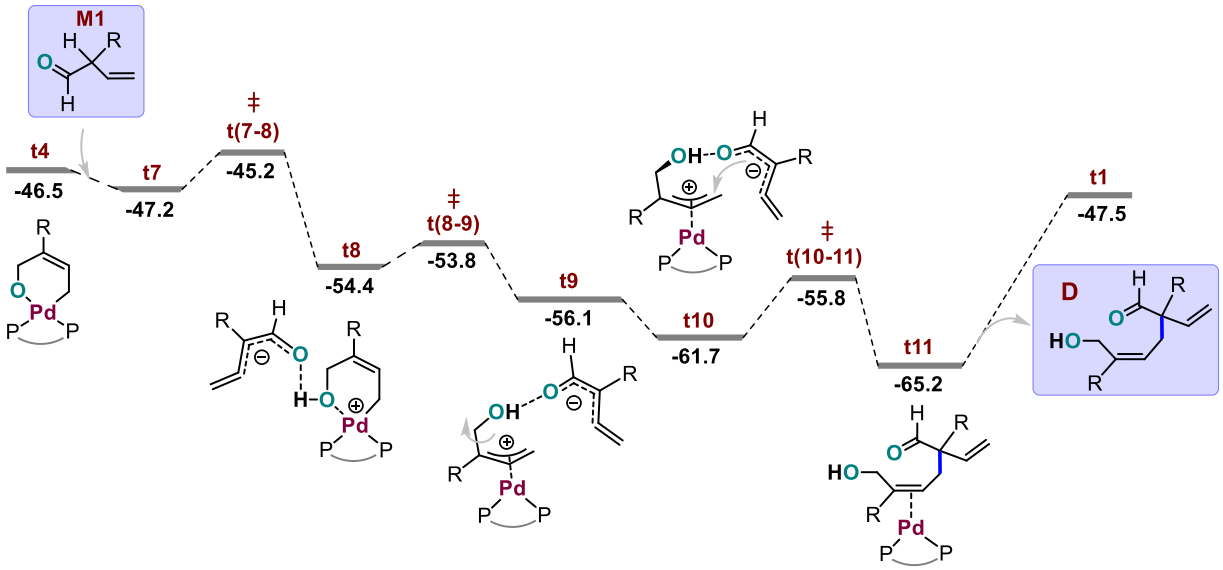


Figure 5. Free energy profile (kcal/mol) for the second part of the catalytic cycle leading to the departure of aldehyde product **D**.

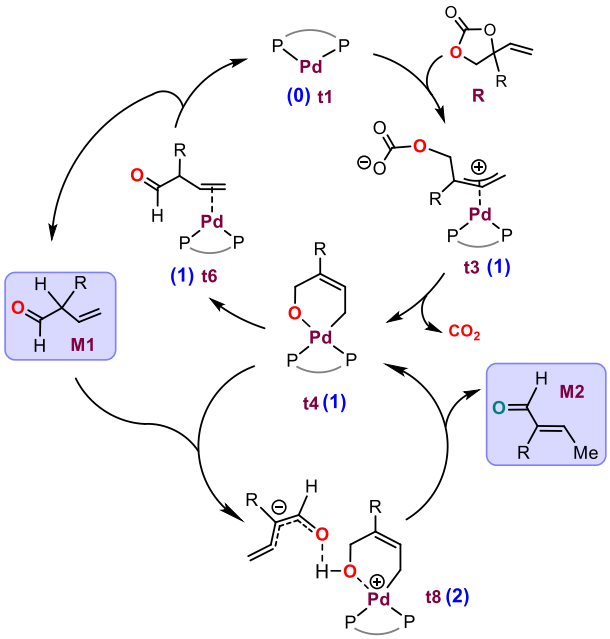
A second molecule of **R** is consumed to generate **t4** which then reacts with **M1** to produce intermediate **t8** (Scheme 2 and Figure 5).[26] Intermediate **t8**, which incorporates two molecules of reactant, can rearrange to intermediate **t11**, and then release the aldehyde product **D** while regenerating the catalyst **t1**. This domino process thus consumes two molecules of reactant **R**, yields product **D** and releases two molecules of CO_2.

In order to understand better the influence of the substituent on the vinyl cyclic carbonate, we also explored the case of the conversion of carbonate **1s** (Figure 2; R^1 = H, R^2 = 2-naphthyl) into the aldehyde **3s**: we found that an alternative cycle dominates as shown in Scheme 3. The cycle differs from the one reported above in the evolution of intermediate **t8**. In this alternative cycle it releases aldehyde **M2** and returns to **t4** with **M2** being significantly more stable than **M1**.[25] This cycle consumes one molecule of reactant **R** and yields product **M2** and one molecule of CO_2. The free energy profiles for all intermediates in this alternative cycle are provided in the SI.

It is difficult to predict product distribution merely based on the free energy profiles in such a complicated cycle, and thus we used micro-kinetic models.[27] The free energy profiles were utilized to compute rate constants and equilibrium constants for each step, and calculation from the starting concentrations used in experiment were performed. The result of this micro-kinetic modeling is a prediction of the ratio of aldehyde products (type **2** *vs* **3**) of 88:12 when using carbonate **1a** and 11:89 upon converting carbonate substrate **1s** (see Tables S1 and S2 in the SI for details). These ratios are close to the experimental observations (90:10 in the case of **1a**, and 7:93 for **1s**) suggesting the validity of our mechanistic proposal. The product ratio follows the order of the relative energies of the exit channels from equilibrium as mentioned above.

We examined the associated structures in search of a qualitative explanation for the product selectivity. There is no obvious steric influence from phenyl/2-naphthyl replacement in any of the intermediate structures, as the additional ring in naphthyl fragment points in all cases away from the rest of the atoms. In contrast, electronic effects are very likely to exert an influence in the structure of transition state **t(4-5)** in the exit channel leading to product **M2** (see Figure S3 in SI). In this transition state, shown in Figure 6 for the system containing a 2-naphthyl substituent, there is a hydrogen transfer between two carbon centers. One of these carbon centers, which changes its hybridization, is adjacent to the naphthyl group, and this should account for a strong electronic influence. There is no such obvious electronic dependence in the exit channel leading to product **D** (see Figure S3 in SI). Thus, electronic effects are likely the key to the chemoselectivity towards either aldehyde products **2** or **3**. This is indeed consistent with the experimental results, where reactant **1n** (with a MeO-naphthyl substituent) was shown to behave similarly to **1a** despite the similar steric impediments of substrates **1n** and **1s**.

Scheme 3. Simplified Catalytic Cycle for the Conversion of Carbonate 1s Derived from the DFT Calculations. The Numbers in Parentheses Highlight the Number of Reactant Fragments Included in Each Species



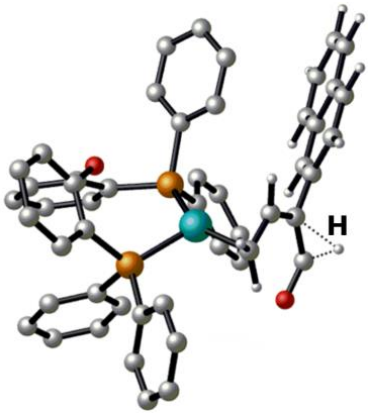


Figure 6. Optimized structure of transition state **t(4-5)s**. The hydrogen atom most involved in the reaction coordinate is highlighted with a label. Most other hydrogen atoms are omitted for clarity.

CONCLUSION

In summary, we herein report an interesting Pd-catalyzed decarboxylative domino process enabling the synthesis of vinyl scaffolds with highly functionalized quaternary carbon centers. In most cases, the reaction can be performed at room temperature without any additives. This protocol also features the *in situ* formation of synthetically attractive aldehyde and (*Z*)-configured polysubstituted allylic alcohol fragments in a single step from readily available and modular vinyl cyclic carbonates. These highly functionalized products are useful building blocks as exemplified by several synthetic transformations. DFT calculations provide a rationale and suggest a complex mechanism where subtle electronic effects are able to modify the nature of the major product of the reaction. These findings shed light on the development of new catalytic domino reactions for challenging Csp^3-Csp^3 bond formations via decarboxylative methodologies under mild reaction conditions.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxx.

Experimental/DFT details and characterization data (PDF), Crystallographic data for **2d** (in CIF format)

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Notes

The authors declare no competing financial interest. A data set collection of computational results is available in the ioChem-BD repository.[28]

ACKNOWLEDGEMENTS

We thank CERCA Programme/Generalitat de Catalunya, ICREA, and the Spanish MINECO through projects CTQ2014-57761-R, CTQ-2014–60419-R, Severo Ochoa Excellence Accreditation 2014–2018 through project SEV-2013–0319 and Severo Ochoa/FPI fellowship to J.E.G. Dr. Eddy Martin and Eduardo C. Escudero-Adán are acknowledged for the X-ray analysis.

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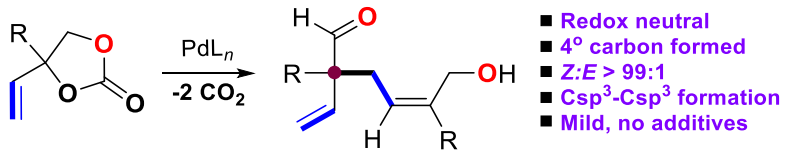
R
O
O
O
PdL$_n$
-2 CO$_2$
H
O
R
OH
H
R
■ Redox neutral
■ 4° carbon formed
■ *Z:E* > 99:1
■ Csp^3-Csp^3 formation
■ Mild, no additives