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Pd-Catalyzed Decarboxylative Olefination: Stereoselective Synthesis of Polysubstituted Butadienes and Macrocyclic P-glycoprotein Inhibitors

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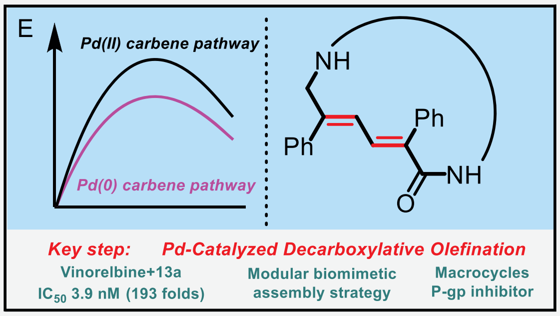
ABSTRACT: The efficient and stereoselective synthesis of polysubstituted butadienes, especially the multifunctional butadienes, represents a great challenge in organic synthesis. Herein, we wish to report a distinctive Pd(0) carbene-initiated decarboxylative olefination approach that enables the direct coupling of diazo esters with vinylethylene carbonates (VECs), vinyl oxazolidinones, or vinyl benzoxazinones to afford alcohol-, amine-, or aniline-containing 1,3-dienes in moderate to high yields and with excellent stereoselectivity. This protocol features operational simplicity, mild reaction conditions, a broad substrate scope, and gram-scalability. Notably, a structurally unique allylic Pd(II) intermediate was isolated and characterized. DFT calculation and control experiments demonstrated that a rare Pd(0) carbene intermediate could be involved in this reaction. Moreover, the polysubstituted butadienes as novel building blocks were unprecedentedly assembled into macrocycles, which efficiently inhibited the P-glycoprotein and dramatically reversed multidrug resistance in cancer cells by 190-fold.



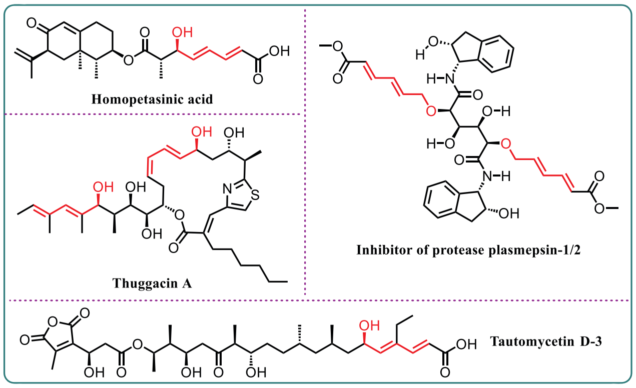
INTRODUCTION

The Pd-catalyzed cross-coupling reaction between electrophiles and diazo compounds has emerged as a versatile and reliable tool for olefination via subsequent Pd(0) oxidative addition of a C−X (X = carbon, nitrogen, halides, etc.) bond, migratory insertion, and β-hydride elimination.[1] In this context, the hypothesis of a Pd(II) carbene pathway has been widely accepted and investigated.[1] In contrast, an alternative Pd(0) carbene manifold has comparatively been underexploited in this field, although it could hold great promise for the development of novel transformations. The distinction between these two pathways is the sequence of diazo decomposition, which is determined by the activation energy. Undoubtedly, a deep understanding of the Pd carbene pathway and the design of Pd carbene trappings have become two overarching goals toward the continuing development of carbene cross-coupling chemistry.

Alcohol-, amine-, or aniline-containing 1,3-dienes are structural motifs in a wide range of natural products[2] and biologically active molecules[3] (Scheme 1). Moreover, these 1,3-dienes could serve as versatile handles for further complex molecule elaboration[4] owing to their multifunctional groups and ease of manipulation, such as construction of macrocyclic compounds, and they have received much attention from the synthetic community.[5,6]

Recently, Loh and Xu reported Pd-catalyzed oxidative cross-coupling which can provide trisubstituted (2*E*,4*Z*)-configured alcohol-containing 1,3-dienes[6d] (Scheme 2b). However, the construction of bulkier tetrasubstituted (2*E*,4*E*)-configured alcohol- and amine-containing 1,3-dienes was not successful.

Scheme 1. Natural Products and Pharmaceutical Molecules with Alcohol- or Ether-Containing 1,3-Dienes



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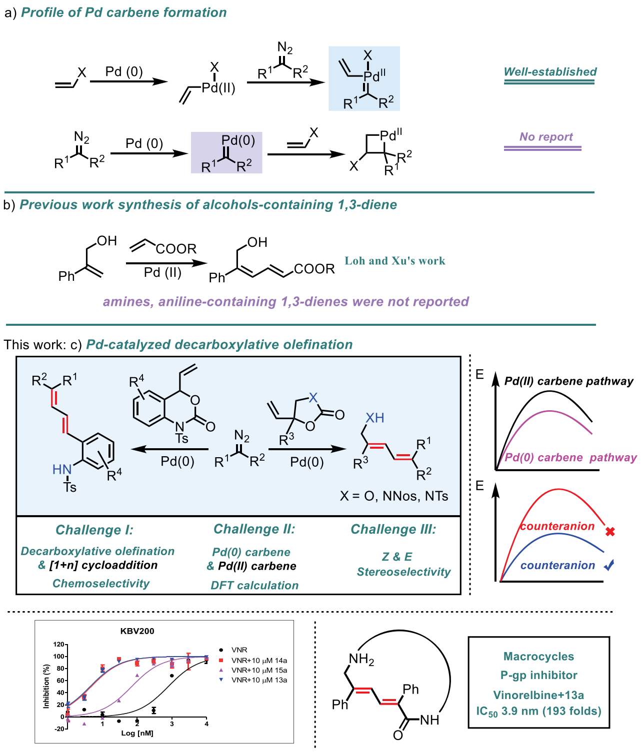
Scheme 2. Profile of Pd Carbene Formation and Our Designs



Thus, from the viewpoints of sustainable synthesis and new drug discovery, a general and simple method for rapidly assembling, structurally diverse, and alcohol-, amine-, or aniline-containing 1,3-dienes is desirable.

Stimulated by those pioneering studies on Pd-catalyzed carbene coupling reactions and our previous works on Pd-catalyzed allylic transformations,[7] we envisioned that vinylethylene carbonates (VECs), vinyl oxazolidinones, or vinyl benzoxazinones could be applied as new Pd-carbene trappings. If successful, such a protocol would not only provide a unique opportunity to learn more about Pd(0) or Pd(II) carbene reaction pathways but also represent a powerful technique for accessing our multifunctional-group-containing 1,3-dienes targets. However, there are three challenging issues to be addressed in these scenarios: (a) Pd-catalyzed chemoselective [1+*n*] cycloaddition might become the preferable pathway rather than decarboxylative olefination, as it has been very recently demonstrated by Xiao and Lu.[8] (b) Although Pd-catalyzed cycloadditions and allylic substitutions of VECs or vinyl benzoxazinones have been well-established,[8−10] studies on Pd-catalyzed carbene coupling reactions of VECs remain underdeveloped; particularly, DFT calculations of Pd(II) or Pd(0) carbene formation are still lacking to date. (c) Some other methods have been reported to construct the 1,3-diene structure, but they need one configuration-confirmed double bond in the reactant.[6] Different from those methods, in our product two double bonds are newly formed during the reaction, which makes it more difficult to control the stereoselectivity of 1,3-dienes.

Herein, we report the first Pd-catalyzed decarboxylative olefination reaction of VECs and analogs with donor/acceptor carbenes. Accordingly, this palladium-catalyzed transformation enables a highly stereoselective, expeditious synthesis of *E*-configured alcohol-, amine-, and aniline-containing 1,3-dienes. Moreover, polysubstituted butadienes as novel building blocks were successfully assembled into bioactive macrocycles for the first time (Scheme 2c).

■ RESULTS AND DISCUSSION

To examine the feasibility of this reaction, vinylethylene carbonate (**1a**) and methyl 2-diazo-2-phenylacetate (**2a**) were used as model substrates. The elegant work of Kleij[9] and Zhang[10] showed that phosphine ligands are highly effective for Pd-catalyzed cross-coupling of VECs. We first investigated the effect of different phosphine ligands by choosing $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol%) as the catalyst and DMF as solvent at 60 °C (see the Supporting Information (SI)). Screenings of Pd(0) catalysts, diphosphorus ligands, and additives showed that the phosphorus ligands are not required, but *tert*-butylammonium bromide (TBAB) is necessary for the reaction working well. The optimal conditions are $[Pd_2(dba)_3]\cdot CHCl_3$ (2.5 mol%) as Pd source and TBAB (100 mol%) in DMF at 60 °C.

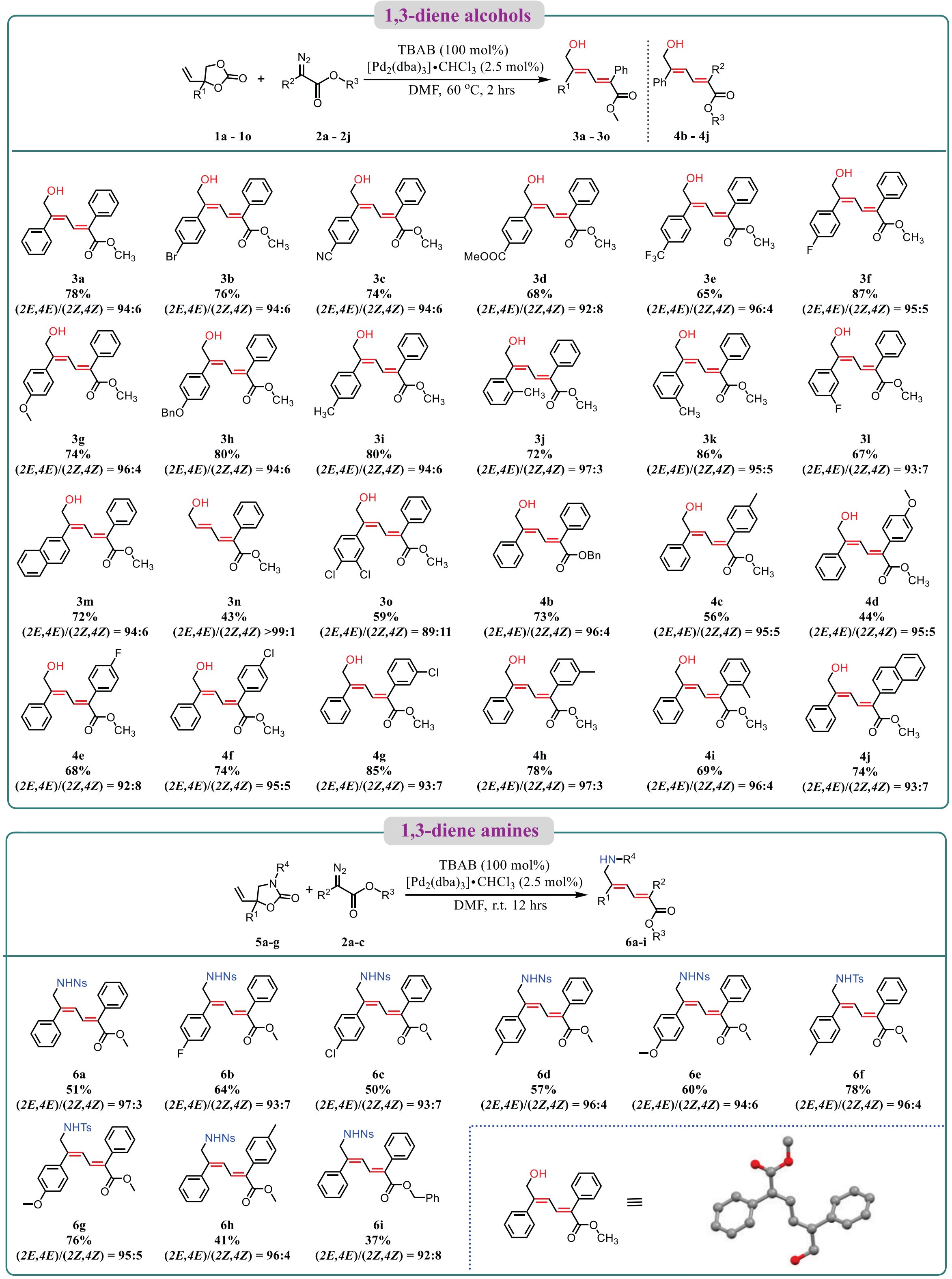
With the optimal conditions in hand, we evaluated various VECs in the Pd-catalyzed decarboxylative olefination reactions with methyl 2-diazo-2-phenylacetate (**2a**) (Table 1). The newly developed protocol gave excellent stereoselectivities in most cases, with *E*/*Z* ratios more than 94:6 and moderate to very good isolated yields. Functional groups on the rings such as cyano (**1c**), ester (**1d**), trifluoromethyl (**1e**), methoxyl (**1g**), and methyl (**1i**) were tolerated well, furnishing the desired products in moderate to good yields. A useful brominated arene was converted (**1b**), thereby providing a versatile handle for subsequent chemical transformations. Additionally, the process was not hampered by ortho substitution (**1j**). Furthermore, the phenyl ring was successfully replaced by 2-naphthyl, without an obvious erosive effect on reaction efficiency and stereoselectivity (**1m**). Switching aryl to hydrogen was also compatible with this reaction, generating almost solely the isomer albeit with 46% yield (**1n**). Even the disubstituted aryl was amenable to the standard conditions, and the expected product was formed with a satisfactory yield of 59% (**1o**).

The diazo compound scope was also investigated. As illustrated in Table 1, phenyl-containing electron-donating or electron-withdrawing groups were efficiently accommodated to yield conjugated allylic alcohols in moderate to good yields and with high stereoselectivities.

We then extended our strategy to the cross-coupling of vinyloxazolidin-2-ones with diazo compounds. The direct coupling reaction proceeds smoothly to afford the conjugated allylic amines in moderate to good yields and high stereoselectivities at room temperature. Those vinyloxazolidin-2-ones bearing electron-donating or electron-withdrawing phenyl substituents successfully participated in the reaction, giving the corresponding products in moderate to good yields with *E*/*Z* stereoselectivities ranging from 92:8 to 97:3, as shown in Table 1. Both the Tosyl and the Nosyl protecting groups were compatible in this reaction. However, the unprotected substrate failed to yield the expected product, possibly due to strong coordination to the Pd catalyst.

This protocol was also compatible with the construction of the trisubstituted *E*-configured multifunctional aniline-containing 1,3-dienes when we changed the vinyloxazolidin-2-ones to vinyl benzoxazinones. This decarboxylative olefination is distinct from Xiao and Lu's recent work, in which they described an intriguing Pd-catalyzed [4+2] cycloaddition of vinyl benzoxazinones with a diazo ketone under visible light photoactivation conditions.[8b] As shown in Table 2, various

Table 1. Substrate Scope for Pd-Catalyzed Synthesis of Tetrasubstituted *E*-Configured Alcohol- and Amine-Containing 1,3-Dienes[a]

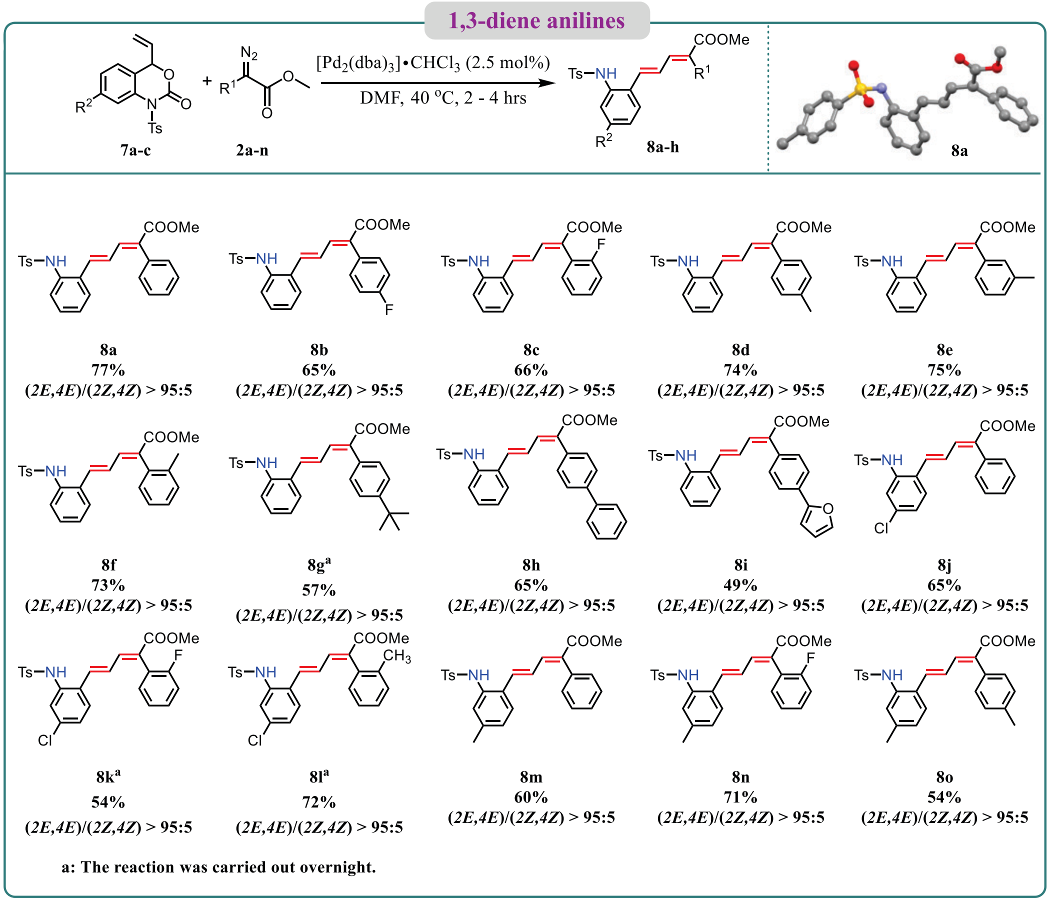


3a 78% (2*E*,4*E*)/(2*Z*,4*Z*) = 94:6
3b 76% (2*E*,4*E*)/(2*Z*,4*Z*) = 94:6
3c 74% (2*E*,4*E*)/(2*Z*,4*Z*) = 94:6
3d 68% (2*E*,4*E*)/(2*Z*,4*Z*) = 92:8
3e 65% (2*E*,4*E*)/(2*Z*,4*Z*) = 96:4
3f 87% (2*E*,4*E*)/(2*Z*,4*Z*) = 95:5
3g 74% (2*E*,4*E*)/(2*Z*,4*Z*) = 96:4
3h 80% (2*E*,4*E*)/(2*Z*,4*Z*) = 94:6
3i 80% (2*E*,4*E*)/(2*Z*,4*Z*) = 94:6
3j 72% (2*E*,4*E*)/(2*Z*,4*Z*) = 97:3
3k 86% (2*E*,4*E*)/(2*Z*,4*Z*) = 95:5
3l 67% (2*E*,4*E*)/(2*Z*,4*Z*) = 93:7
3m 72% (2*E*,4*E*)/(2*Z*,4*Z*) = 94:6
3n 43% (2*E*,4*E*)/(2*Z*,4*Z*) >99:1
3o 59% (2*E*,4*E*)/(2*Z*,4*Z*) = 89:11
4b 73% (2*E*,4*E*)/(2*Z*,4*Z*) = 96:4
4c 56% (2*E*,4*E*)/(2*Z*,4*Z*) = 95:5
4d 44% (2*E*,4*E*)/(2*Z*,4*Z*) = 95:5
4e 68% (2*E*,4*E*)/(2*Z*,4*Z*) = 92:8
4f 74% (2*E*,4*E*)/(2*Z*,4*Z*) = 95:5
4g 85% (2*E*,4*E*)/(2*Z*,4*Z*) = 93:7
4h 78% (2*E*,4*E*)/(2*Z*,4*Z*) = 97:3
4i 69% (2*E*,4*E*)/(2*Z*,4*Z*) = 96:4
4j 74% (2*E*,4*E*)/(2*Z*,4*Z*) = 93:7
6a 51% (2*E*,4*E*)/(2*Z*,4*Z*) = 97:3
6b 64% (2*E*,4*E*)/(2*Z*,4*Z*) = 93:7
6c 50% (2*E*,4*E*)/(2*Z*,4*Z*) = 93:7
6d 57% (2*E*,4*E*)/(2*Z*,4*Z*) = 96:4
6e 60% (2*E*,4*E*)/(2*Z*,4*Z*) = 94:6
6f 78% (2*E*,4*E*)/(2*Z*,4*Z*) = 96:4
6g 76% (2*E*,4*E*)/(2*Z*,4*Z*) = 95:5
6h 41% (2*E*,4*E*)/(2*Z*,4*Z*) = 96:4
6i 37% (2*E*,4*E*)/(2*Z*,4*Z*) = 92:8

[a] Reaction conditions: vinylethylene carbonates/vinyloxazolidin-2-ones (0.1 mmol), diazo compounds **2** (0.2 mmol), Pd catalyst (5 mol%), TBAB (0.1 mmol), DMF (1 mL). The *E*/*Z* ratio was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as an internal standard. All the yields are isolated yields.

para-, *meta*-, or *ortho*-substituents on the substituted diazo esters could be well tolerated to provide the desired products in moderate to good yields of exclusively the *E*-configured isomer. The furanyl-substituted diazo ester reacted smoothly to produce

Table 2. Substrate Scope for Pd-Catalyzed Synthesis of Trisubstituted *E*-Configured Aniline-Containing 1,3-Dienes[a]



8a 77% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8b 65% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8c 66% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8d 74% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8e 75% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8f 73% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8g[a] 57% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8h 65% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8i 49% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8j 65% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8k[a] 54% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8l[a] 72% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8m 60% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8n 71% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

8o 54% (2*E*,4*E*)/(2*Z*,4*Z*) > 95:5

a: The reaction was carried out overnight.

[a] Reaction conditions: 2*H*-benzo[*d*][1,3]oxazin-2-ones (0.05 mmol), diazo compounds **2** (0.1 mmol), Pd catalyst (5 mol%), DMF (0.5 mL). All the yields are isolated yields.

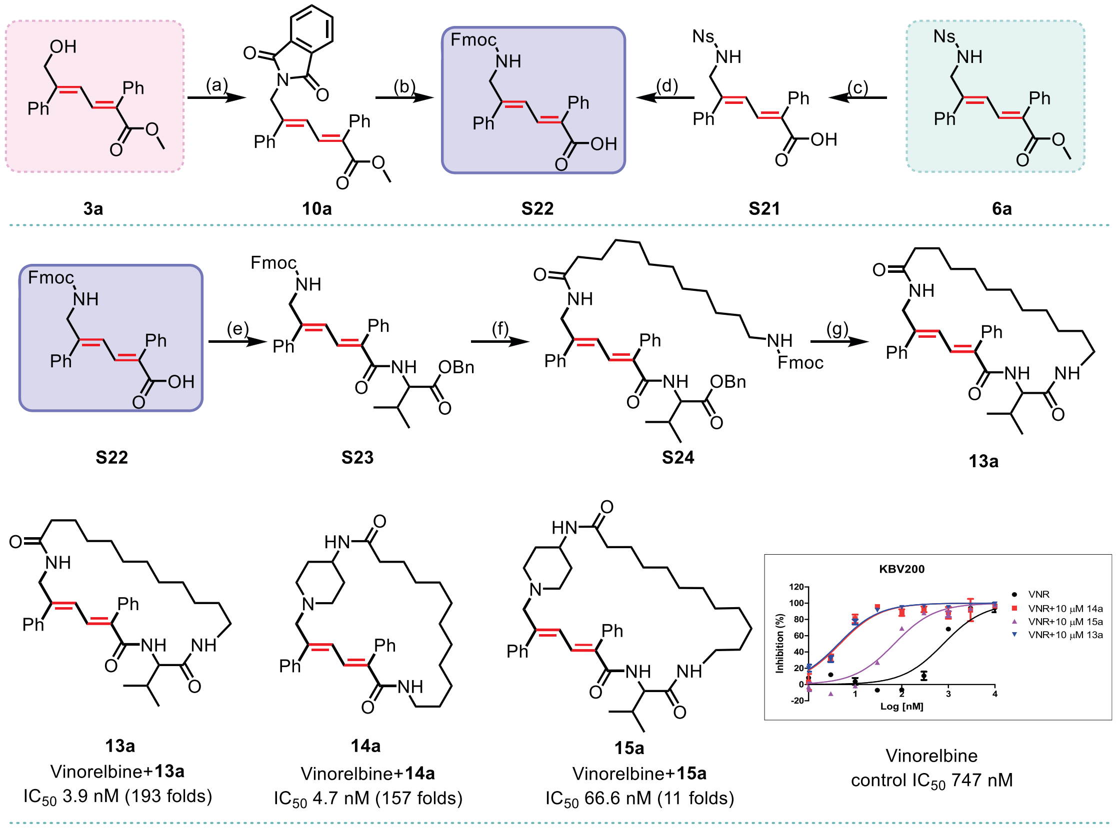
8i in a synthetically useful yield. In addition, two typical vinyl benzoxazinone partners also efficiently engaged in this olefination, regardless of the electronic properties on the substrates, to deliver **8j**−**8o** in good isolated yields. Generally, our method could only produce 1,4-diaryldienes, except for one example, **3n**.

The synthetic value of this catalytic system was next demonstrated through a large-scale reaction and product derivatizations. The gram-scale reaction of **1a** and **2a** afforded the conjugated allylic alcohol **3a** with excellent *E*/*Z* stereoselectivity (95:5) and very good isolated yield (79%, SI Figure 16). The selective oxidation of a hydroxyl moiety of **3a** by treatment with Dess−Martin periodinane (DMP) can afford conjugated aldehyde **9a**, which is an important building block to construct luminescent materials. In addition, **3a** was successfully converted into the highly conjugated allylic amine **10a** by the Mitsunobu reaction. Selective epoxidation of the carbon−carbon double bond was also achieved, giving the desired product **11a** in 93% yield. Furthermore, a symmetrical conjugated allylic diol could be prepared by the reduction of **3a** with DIBAL-H in a good yield (SI Figure 16).

Interestingly, we found that the structures from our method could be used as building blocks in drug discovery as well. As mentioned above, 1,3-dienes are important structural motifs found in a number of biologically active natural products, particularly in macrocycles. Encouraged by this fact, we attempted to construct 1,3-diene-supported macrocycles by using **3a** or **6a** as a building block. With five steps, three novel macrocycles—**13a**, **14a**, and **15a**—were efficiently assembled (Scheme 3). To explore whether these 1,3-diene-supported macrocycles could successfully transfer pharmacologically relevant features, the effects of the collected compounds on reversing multidrug resistance[11] to chemotherapeutic agents were evaluated using human oral epidermoid carcinoma KB and their drug-resistant counterpart KBV200 cells with P-gp overexpression. To our delight, both **13a** and **14a** exhibited excellent potency, with an IC$_{50}$ of 3.9 and 4.7 nM, respectively. Moreover, they could restore the sensitivities of KBV200 cells to cytotoxic agent vinorelbine with 193-fold and 157-fold reversals, respectively. Undoubtedly, these promising results highlighted that our protocol is unique and has potential in lead compounds discovery. Further, we believe our structure will have wide applications in drug discovery for other diseases.

The high (2*E*,4*E*) stereoselectivity of this Pd-catalyzed-decarboxylative olefination attracted our attention; we found that no isomerization of the products was observed under the standard conditions. The two newly formed double bonds of the 1,3-dienes are probably controlled by *β*-O and *β*-H eliminations (Figure 1). TBAB is much more effective than other less sterically hindered additives, such as TMAB, TEAB, or no additive, for which the *E*/*Z* stereoselectivities have declined (Table 3). Besides the steric effect improving the stereoselectivities, the fact is that counteranions, such as bromide and chloride, have proven to be crucial to improve the reaction yield

Scheme 3. Construction of Novel Macrocycles and Their Bioactivity on Reversing P-gp-Mediated Multidrug Resistance in Cancer Cells Using (2*E*,4*E*)-1,3-Diene Building Blocks



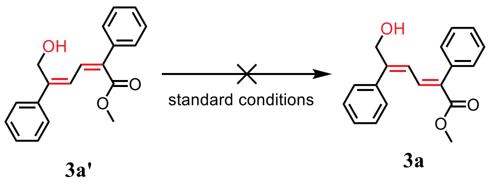


Figure 1. Isomerization experiments between *E*-isomer and *Z*-isomer.

Table 3. Effects of Counteranions on the Reaction

entry	catalyst	additive	yield	$\frac{(2E,4E)}{(2E,4E) + (2Z,4Z)}$
1	$[Pd_2(dba)_3]\cdot CHCl_3$	–	49%	80.8% ± 1.2%
2	$[Pd_2(dba)_3]\cdot CHCl_3$	TBAB	78%	93.7% ± 0.7%
3	$[Pd_2(dba)_3]\cdot CHCl_3$	TEAB[a]	68%	90.9% ± 0.7%
4	$[Pd_2(dba)_3]\cdot CHCl_3$	TMAB[b]	68%	89.1% ± 1.9%
5	$Pd_2(dba)_3$	TBAB	71%	92.2% ± 1.2%
6	$Pd_2(dba)_3$	–	14%	80.8% ± 5.2%

[a] TEAB = tetraethylammonium bromide. [b] TMAB = tetramethylammonium bromide.

as well as the stereoselectivity, which is in consistent with our DFT calculations (see the following part or SI). Moreover, kinetic studies show that the initial reaction rate will decrease with increasing addition of TBAB (Figure 2), because excess counteranion Br is harmful for *β*-H elimination[12] (SI Figure 13). The overall reaction is nearly zero order with respect to vinylcarbonate **1a** (SI Figure 3), which could provide support for the initial formation of Pd(0)-carbene intermediate **IN3** via diazo decomposition of **2a** (see Figure 4).

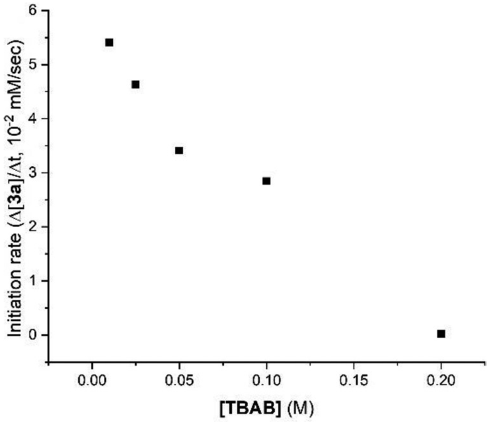


Figure 2. Kinetics experiments of TBAB.

To investigate the initiation of the reaction, a series of control experiments were carried out (Figure 3). First, we separately submitted VEC (**1a**) and diazo ester **2a** to the standard conditions, but using stoichiometric $[Pd_2(dba)_3]\cdot CHCl_3$. Although no conversion took place for **1a** in the absence of diazo ester **2a**, oxidative addition of Pd(0) with **1a** could occur to form a reversible Pd(II) intermediate (Figure 3, Eq. 1). Interestingly, a complete conversion of **2a** and dba ligand exchange were observed from NMR analysis. Meanwhile, methyl 2-oxo-2-phenylacetate, an oxidation product of carbene, was separated and identified by ^{1}H NMR (Figure 3, Eq. 2). Combining a catalytic amount of **2a** (20%) with stoichiometric **1a** and $[Pd_2(dba)_3]\cdot CHCl_3$ gave the olefination product **3a** in 40% NMR yield (Figure 3, Eq. 3). The results above showed that

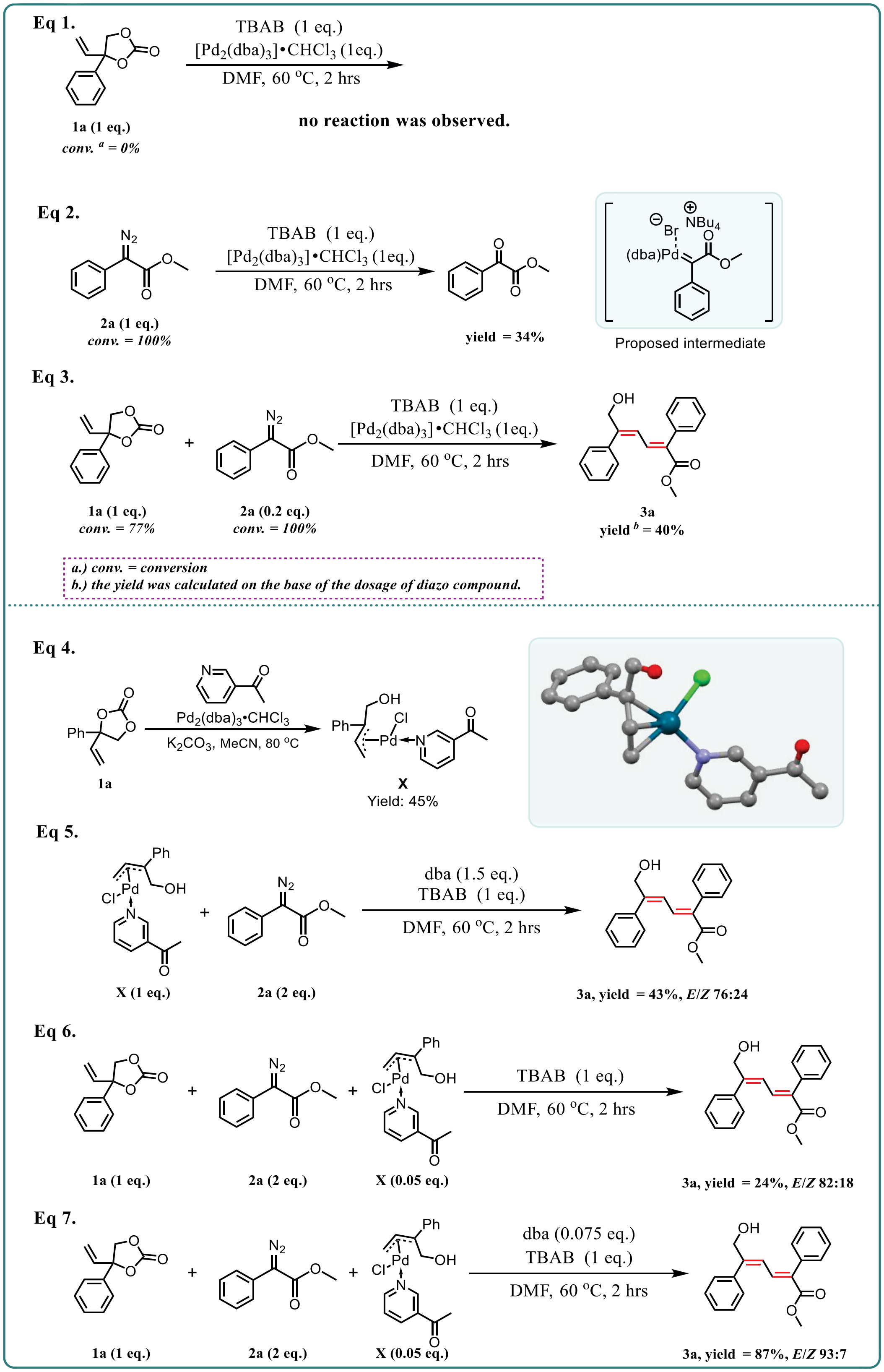


Figure 3. Mechanistic experiments.

the reaction could be initiated by Pd(0) carbene intermediate generated from direct diazo decomposition of **2a**, but we could not clearly exclude the Pd(II) carbene intermediate pathway initiated from oxidative addition of Pd(0) with VECs.

Due to the instability of the Pd(0) carbene intermediate, we attempted to capture the π-allyl Pd(II) intermediate acting as a precursor of Pd(II) carbene instead, which we have successfully isolated in our previous work.[7c] The π-allyl Pd(II) intermediate

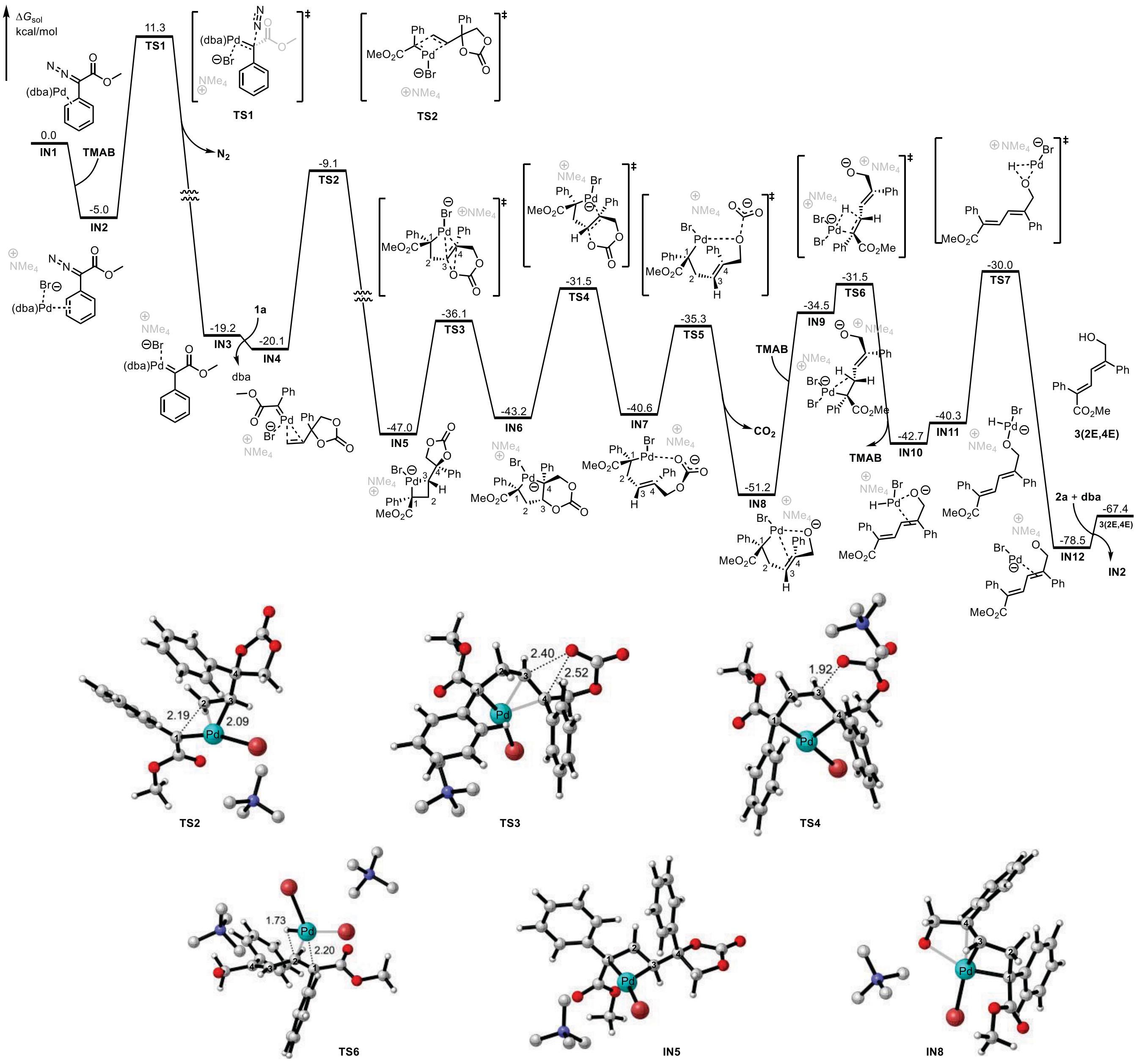


Figure 4. DFT-computed potential energy surface and geometric structures for key species for the Pd-catalyzed reactions between **1a** and **2a**. All hydrogens on the NMe_4 ion are omitted for clarity; selected distances are in Å.

has been stabilized with pyridine ligand (Figure 3, Eq. 4) and fully characterized by ^1H and ^{13}C NMR and X-ray spectroscopy. With the π-allyl Pd(II) intermediate in hand, a set of experiments were conducted to further elucidate the possible pathway of the reaction. If the π-allyl Pd(II) intermediate, a precursor of Pd(II) carbene, makes the reaction sluggish, then the Pd(II) carbene pathway could be a less preferable one. Gratifyingly, when a stoichiometric amount of the π-allyl Pd(II) intermediate was subjected to the reaction with **2a**, the yield and stereoselectivity of **3a** were profoundly decreased (Figure 3, Eq. 5). Further, in order to eliminate concerns about the effect of strong coordination between pyridine and Pd(II) intermediate and keep consistent with the standard conditions, additional two control experiments were carried out (Figure 3, Eqs. 6 and 7). Notably, the results demonstrated that the presence of pyridine ligand might not be the crucial factor in the decreased yield and stereoselectivity. It is more likely that the Pd(II)-allyl complex causes the retarding effect on the final yield/selectivity. Altogether, we could conclude that it is more likely for the reaction to be initiated by the Pd(0) carbene intermediate generated from direct diazo decomposition of **2a** instead of the oxidative addition of Pd(0) to VEC (**1a**).

Notably, except for the NHC palladium(0) complex,[13b−h] other reactive Pd(0) carbene intermediates[13a] are rarely reported in comparison with ubiquitous high-valent metal carbene species such as Pd(II),[1] Cu(I),[14] Rh(II),[15] Ir(I),[16] etc. To further investigate the reaction mechanism, a series of DFT calculations were conducted at the level of (SMD)M06/6-311+G(d,p)/SDD//M06/6-31G(d)/LANL2DZ, using 4-phenyl-4-vinyl-1,3-dioxolan-2-one (**1a**) and methyl 2-diazo-2-phenylacetate (**2a**) as the model reactants.[17] Calculations found that if the $Pd_2(dba)_3$ was used as the catalyst without any additive, a very high activation barrier of 36.3 kcal/mol was found for the β-hydrogen elimination step (see SI Figure 8 for details). This prediction correlates well the experimental observations (Table 3, entry 6). However, in the reaction with the $[Pd_2(dba)_3]\cdot CHCl_3$ catalyst, the yield of product **3** was increased to 49% (Table 3, entry 1), indicating notable promoting effects of the complexed $CHCl_3$ molecule. Inspired by the results of the control experiment (Table 3, entries 1 and 6), showing that $CHCl_3$ could act as the source of the chloride in the intermediate as well as the intermediate **X** (Figure 3, Eq. 4), as we have reported in our previous work,[7c] we proposed that the bromide anion from TBAB additive may be involved as a ligand to Pd to promote the reactions. Indeed, when TMAB—a simplified model for TBAB—was included in calculations to simulate the effects of the quaternary ammonium salt additive on the reaction, initiation by generation of the Pd(0) carbene species was found to be the most favorable (the other Pd(II) initiation pathway calculated in SI Figure 7), from which the observed product **3a** (2*E*,4*E*) could be formed with reasonable energy values (Figure 4).

On the other hand, the calculated energies show that the pathway leading to the minor product **3** (2*Z*,4*Z*) is less favorable kinetically (Figure 5), in good agreement with the observed stereoselectivity. Other possible competing reactions are higher in energy and are given in SI Figure 9.

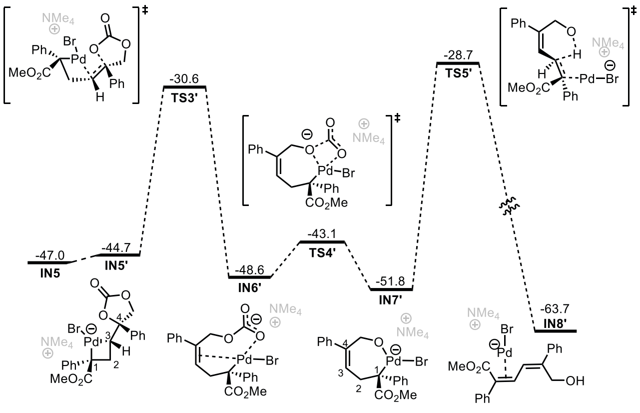


Figure 5. DFT-computed potential energy surface for the formation of **3a** (2*Z*,4*Z*) from **IN5**.

Accordingly, the association of reactant complex **IN1** with TMBA forms **IN2** favorably, from which the dinitrogen elimination occurs via **TS1** with a barrier of only 16.3 kcal/mol and gives rise to Pd(0) carbene species **IN3** exergonically. After incorporation of **1a**, π complex **IN4** is formed slightly exergonically. In the following step, we found that the olefin favors [2+2] cycloaddition with the Pd=C moiety (via **TS2**) to form intermediate **IN5** containing a four-membered ring.[18] In **IN5**, the Pd−C3 and C4−O bonds are anti to each other (Figure 4). We failed to locate a TS for direct cleavage of the C4−O bond to form a zwitterionic intermediate. Instead, calculations revealed that **IN5** undergoes ring expansion rearrangement easily by a concerted 1,2-oxygen/1,2-palladium migration via **TS3** (C3−O = 2.40 Å and C4−O = 2.52 Å) to form bicyclic intermediate **IN6** (Figure 4). This intermediate is slightly less stable than **IN5** and undergoes C3−O bond cleavage via **TS4** to form ionic species **IN7**, which eliminates the CO_2 via **TS5**, giving rise to intermediate **IN8** through an exergonic process. Both steps are very facile, with barriers less than 10 kcal/mol. As determined by the configuration of **IN6**, the newly formed double bond in **IN7** adopts the *E* configuration. **IN8** is a homoallylic palladium complex in which the Pd is intramolecularly coordinated by the oxygen anion. Prior to the β-H elimination, the incorporation of another TMAB is necessary to form **IN9** via an endergonic process.[19] **IN9** has a C−H···Pd agostic interaction and undergoes facile stereoselective β-H elimination via **TS6** (C2−H = 1.73 Å and C1−Pd = 2.20 Å), generating intermediate **IN10** with the expected stereochemistry of the 1,3-diene moiety. Further calculations indicate that the final product **3a** (2*E*,4*E*) could be formed by reductive elimination of the palladium hydride species (**IN10** and **IN11**).

Due to the endergonicity for regeneration of **IN2** from **IN12** (11.1 kcal/mol), the overall activation barrier for the reaction should be 27.4 kcal/mol, as determined by the energy change for the process **IN12** → **IN2** → **TS1**. This is the highest barrier for the whole reaction, indicating that the dinitrogen elimination via **TS1** is the rate-determining step of the reaction. In addition, the β-H elimination process is from **TS6** to **IN10** (Figure 4), for which the syn-coplanar arrangement of Pd−C−C−H is necessary as well as TMAB dissociating from the catalyst to afford an empty orbital of Pd. If excess counteranion Br is present, the formation of a coordination-saturated Pd complex (given in SI Figure 13), instead of **IN9**, will make the elimination process sluggish, in agreement with the kinetic experiment with respect to TBAB.[12]

To generate the minor product **3a** (2*Z*,4*Z*), a less stable conformer **IN5′** could be first formed by rotation of the C−C single bond connecting the two rings in **IN5** (Figure 5). From **IN5′** the cleavage of C4−O and C3−Pd bonds occurs in concerted to form a nine-membered-ring intermediate, **IN6′**, in which the newly formed C−C double bond adopts the *Z* configuration. In the following step, decarboxylation occurs via **TS4′** to generate **IN7′**. Finally, β-H elimination is completed by an intramolecular hydrogen transfer from C2 to O via **TS5′** to afford product complex **IN8′** exergonically,[18] and the diene moiety has a 2*Z*,4*Z* configuration. In this pathway, the **TS5′** has a highest relative free energy of −28.7 kcal/mol, being 1.3 kcal/mol higher than that of **TS7** on the major pathway. This indicates that formation of **3a** (2*Z*,4*Z*) is less favorable, as both steps from **TS5′** and **TS7** are highly exergonic and irreversible.[17] Thus, the DFT results suggest that the stereochemical outcome of the whole reaction is actually determined by **TS7** and **TS5′** in the last step.

Based on the previous reports,[1,9,10] computational results, and our preliminarily mechanistic experiments, a plausible reaction mechanism for the formation of tetrasubstituted *E*-configured 1,3-dienes containing alcohols is illustrated in Figure 6. The palladium(0) carbene intermediate **IN3** is initially formed through N_2 emission of diazo ester **2a**. The intermediate **IN3** then reacts with VEC **1a** to generate 4-membered palladacycle intermediate **IN5** via a [2+2] intermolecular cycloaddition. Subsequently, the intermediate **IN5** undergoes ring expansion and 1,2-oxygen migration to afford intermediate **IN6**, which then undergoes C−O bond cleavage and CO_2 elimination, followed by β-H elimination to give intermediate **IN10**. Finally, reductive elimination of intermediate **IN10** yields the major geometric isomer **3a** (*E*) and the active Pd(0) for the next catalytic cycle. Alternatively, intermediate **IN5** could form the seven-membered palladacycle intermediate **IN7′**, which eventually provides the minor geometric isomer **3a** (*Z*).

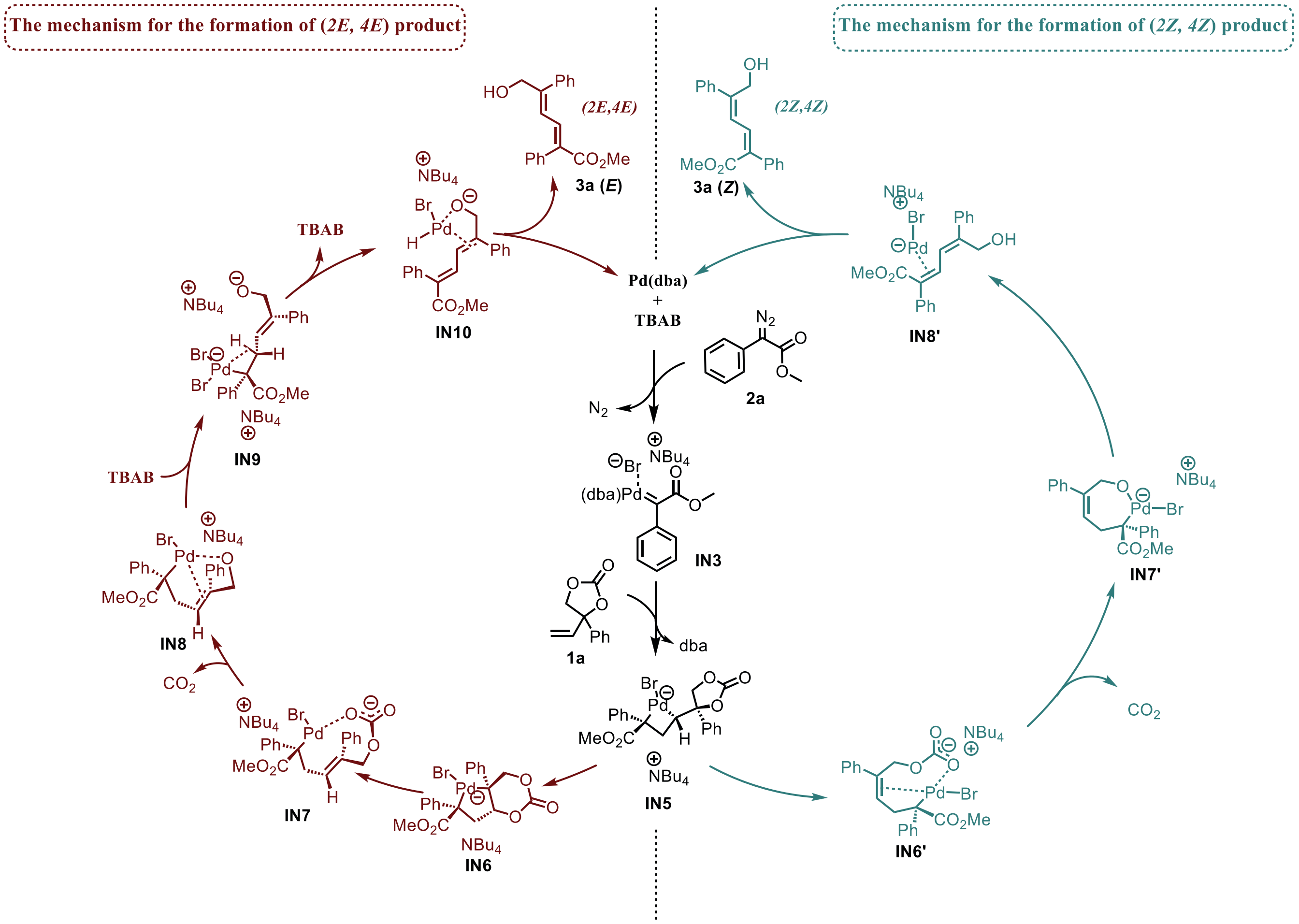


Figure 6. Proposed mechanisms for the formation of tetrasubstituted conjugated *E*- or *Z*-configured 1,3-dienes containing alcohols.[17]

CONCLUSIONS

In summary, we have developed an unprecedented Pd-catalyzed, highly stereoselective decarboxylative olefination of VECs and analogs with donor/acceptor carbenes by a Pd(0) carbene pathway. This strategy provides a practical, user-friendly, and operationally simple protocol for the synthesis of polysubstituted multifunctional *E*-configured 1,3-dienes. Remarkably, our privileged structures—the 1,3-dienes—were successfully incorporated into macrocycles which could fight P-gp-mediated multidrug resistance in cancer chemotherapy with 190-fold reversals. Finally, the mechanism was better understood by a combination of control experiments and DFT calculations, which provided in-depth insights into the counterion effect and stereochemistry of the transformation. More mechanistic investigations on Pd(0) carbene and extensions of this chemistry are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c00078.

Experimental procedures and spectral data for all new compounds (PDF)

X-ray data for compound **3a** (CIF)

X-ray data for compound **8a** (CIF)

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Notes

The authors declare no competing financial interest.

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(17) Computational results in the main text were obtained with the chiral center in **2a** adopting the *R* configuration. It should be noted that the detailed mechanism for reaction with **2a** in *S* configuration is slightly different from that shown in Figures 4 and 5, that the first double bond is formed by the syn-elimination of the corresponding **IN5** to form the **3** (2*E*,4*E*). The diastereoselectivity of the [2+2] cycloaddition and the conformation analysis of **IN5** and **IN5′** and the following elimination TS are given in the Supporting Information.

(18) Analysis of the geometric structures found the **TS2** is favorable with π-π interaction between the two phenyl groups and has less steric effect than other [2+2] cycloaddition TS, which account for the origin of diastereoselectivity in **IN5**. Details are given in SI Figure 10.

(19) Other possible stereoisomers from **IN8** and **IN7′** are given in SI Figure 12a and 12b.