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Mechanism of Palladium/Amine Cocatalyzed Carbocyclization of Aldehydes with Alkynes and Its Merging with "Pd Oxidase Catalysis"

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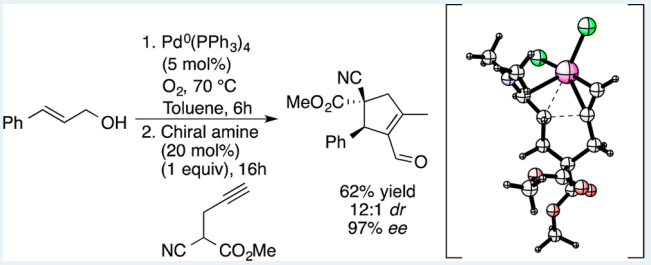
Supporting Information

ABSTRACT: The reaction mechanism for the palladium and amine cocatalyzed carbocyclization of aldehydes with alkynes has been investigated by means of density functional theory calculations and experiments. The Pd/amine cocatalyzed transformation is a carbocyclization of in situ generated enaminynes where the C−C bond-forming step is most likely promoted by a Pd(II) species. Notably, the latent Pd(0)/Pd(II) catalytic redox cycle of this metal/organo cooperative catalytic reaction can be merged with catalytic direct aerobic alcohol oxidation (Pd oxidase catalysis).



KEYWORDS: *carbocyclization, multicatalysis, oxygen, oxidations, relay catalysis, density functional theory*

INTRODUCTION

Cascade and domino reactions that give access to multiple C−C and C−heteroatom bonds are important in Nature and in chemical synthesis.[1] They allow for the synthesis of complex molecular scaffolds in one-pot operations and for the development of green chemistry (e.g., improved *E* factor by reduction of synthetic steps and minimization of waste and solvents).[2] Most of today's disclosed elegant cascade transformations are catalyzed by single chemical entities, which predominantly are transition metals.[3] However, the use of metal-free catalysis has begun to emerge in this research field.[4] The development of selective aerobic oxidations of organic substrates is also an important research area within green chemistry.[5] Here, the catalytic aerobic conversion of alcohols to carbonyl compounds is a potential initial transformation for a catalytic cascade sequence. In particular, the palladium-catalyzed selective direct aerobic oxidations ("Pd oxidase catalysis")[6a] of alcohols, which proceed without the need for an active redox cocatalyst for dioxygen-coupled catalytic turnover,[6] represent an attractive entry for subsequent C−C bond-forming cascade transformations.

Recently, the concept of combining transition-metal catalysis and organocatalysis in one pot ("metal/organo cooperative catalysis") has grown,[7] allowing for the development of new and unprecedented transformations that are not possible by using the transition metal or the organic catalyst alone. Despite these important advantages, there are far fewer metal/organo cooperative catalyzed transformations in comparison to those in which a single catalyst is used. Major factors that contribute to this are the incompatibility between the transition metal and organocatalyst as well as the lack of a mechanistic understanding of these multicatalyst systems. Thus, the mechanistic comprehension of novel cooperative catalytic systems to address these challenges is pressing and important. In 2006, we disclosed that transition-metal catalysis could be combined with aminocatalysis in one pot for achieving C−C bond formation, and since then we have applied this concept to other C−C, C−Si, C−O, C−N, and C−B bond-forming reactions.[8,9] In this context, we recently disclosed highly enantioselective dynamic cooperative dual catalytic systems for the carbocyclization of various catalytically generated enynes (Scheme 1).[9] These enynes are enamine intermediates (enaminynes), which are generated in situ by reversible amine **5** catalyzed conjugate additions of propargyl nucleophiles **1** to enals **2** and are in equilibrium with the Michael products **3**. Next, irreversible C−C bond formation with their alkyne moiety by the synergistic action of a Pd catalyst followed by isomerization of the resulting double bond furnishes the corresponding carbocycles **4** (e.g., cyclopentenes,[9a] dihydrofurans,[9b] dihydropyrrolidines,[9c,10a] or spirolactams[10b]).

While the same type of C−C bond-forming transformation has been proposed to proceed via Lewis acid activation of the alkyne moiety in the presence of other metal catalysts (e.g., Au or Cu salts),[11] there are more mechanistic possibilities for the Pd(0)- or Pd(II)-catalyzed carbocyclizations.[9,10]

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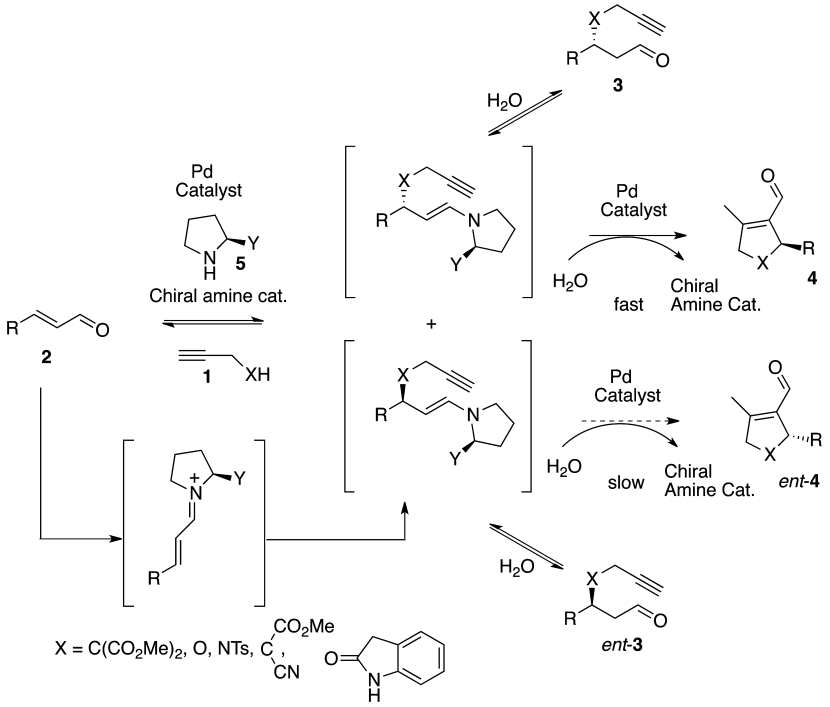
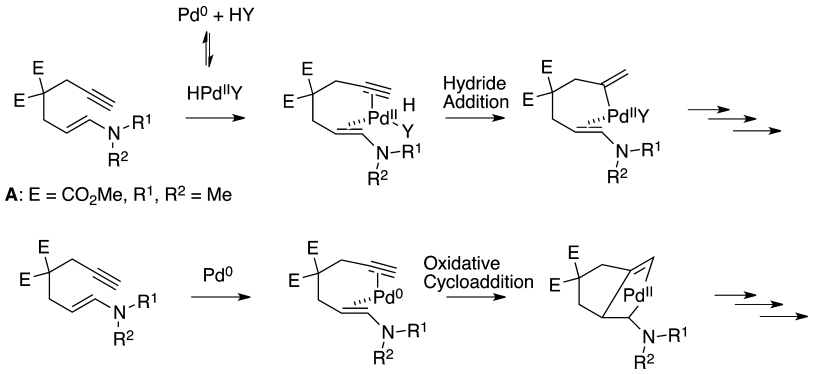
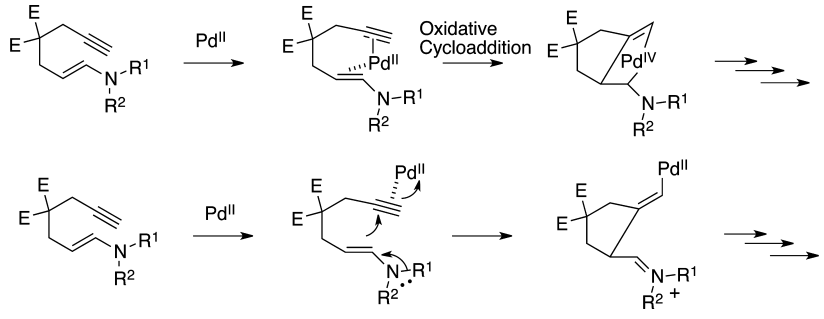
Scheme 1. Pd/Chiral Amine Cocatalyzed Dynamic Kinetic Transformation (DYKAT) between Propargylic Nucleophiles and Enals



Scheme 2. Previously Proposed Mechanisms for the Pd(0)-Catalyzed Carbocyclization[9]



Scheme 3. Previously Proposed Mechanisms for the Pd(II)-Catalyzed Carbocyclization[9,10]



In our initial studies of the Pd(0)-catalyzed carbocyclization of aldehyde-derived enaminynes, two possible initiation mechanisms were proposed: either (1) an oxidative addition of the solvent or a weak acid to palladium(0) to form a Pd(II) hydride species or (2) oxidative cycloaddition between Pd(0) and the enaminyne to form a bicyclic Pd(II) intermediate (Scheme 2).[9a,12] However, the cascade reaction in deuterated solvent did not give the corresponding deuterated products. Thus, the initial oxidative cycloaddition pathway was concluded to be the predominant one under these reaction conditions.[9a]

Another hypothetical reaction mechanism could be that the Pd(0) is converted to a Pd(II) species via a reaction pathway different from that proposed above and then acts as a transition-metal catalyst or a Lewis acid catalyst.[13] Thus, with

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respect to the Pd(II)-catalyzed carbocyclizations, two initial activation pathways were proposed (Scheme 3): either (1) oxidative cycloaddition to form a bicyclic Pd(IV) species[12a] or (2) Lewis acid activation of the alkyne by Pd(II) together with concerted nucleophilic attack by the enamine.

Herein we present experiments together with density functional theory (DFT) calculations to elucidate the mechanism of the C−C bond forming step of the Pd and amine cocatalyzed carbocyclizations of aldehydes with alkynes and its merging with a novel aerobic allylic alcohol oxidation/Michael addition/carbocyclization catalytic relay.

RESULTS AND DISCUSSION

Experimental Studies. We began to investigate the formation of cyclopentene **4a**, which is derived from the **5a** cocatalyzed cascade reaction between propargylic acid ester **1a** and cinnamic aldehyde **2a** in the presence of different Pd catalysts, as a function of time (Figure 1 and eq 1). When

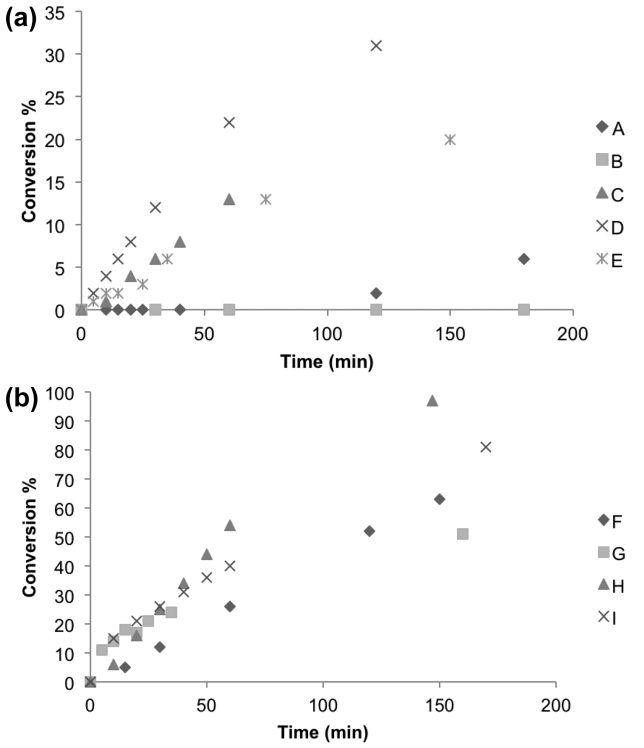
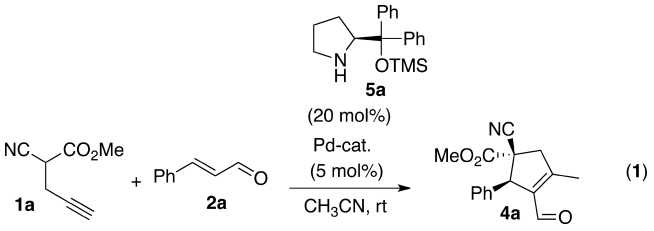


Figure 1. Pd/**5a** cocatalyzed carbocyclization: (A) $Pd(PPh_3)_4$; (B) $Pd(PPh_3)_4$, reaction performed in glovebox, inert atmosphere; (C) $Pd(PPh_3)_4$ prestirred for 2 h under an O_2 atmosphere prior to addition of reactants and **5a**; (D) $PdCl_2$; (E) $PdCl_2$, reaction performed in glovebox, inert atmosphere; (F) $(PPh_3)_2PdO_2$; (G) $(PPh_3)_2PdO_2$, reaction performed in glovebox, inert atmosphere; (H) $Pd^0[P(o\text{-tolyl})_3]_2$; (I) $Pd^0[P(o\text{-tolyl})_3]_2$, reaction performed in glovebox, inert atmosphere. All experiments were performed in CH_3CN. *o*-tolyl = 2-methylphenyl.

$Pd^0(PPh_3)_4$ was used as the metal catalyst, a clear induction time (ca. 2 h) was observed prior to the formation of product **4a** (trace A, Figure 1a). We next performed the $Pd^0(PPh_3)_4$ catalyzed reaction under inert conditions in a glovebox (trace B, Figure 1a). Interestingly, no carbocyclization product **4a** was formed in the absence of oxygen. However, stirring the $Pd^0(PPh_3)_4$ catalyst at ambient temperature under an oxygen atmosphere for 2 h prior to adding **1a**, **2a**, and amine cocatalyst



(1)

5a resulted in immediate cyclopentene **4a** formation (trace C, Figure 1a). The $Pd^{II}Cl_2$-catalyzed carbocyclization to **4a** was fast (trace D, Figure 1a) and also worked under an inert atmosphere (trace E, Figure 1a). In all of the above experiments, the corresponding Michael intermediates **3** were formed, demonstrating that the amine **5a** cocatalyst was active during all conditions investigated (see the Supporting Information).

These experiments demonstrate that the reaction can be catalyzed by a Pd(II) species. Moreover, they show that the presence of molecular oxygen is necessary when $Pd^0(PPh_3)_4$ is used as the palladium source. Since Pd(II) species are active as catalysts, one possible explanation for this observation is that the oxidation of Pd(0) to Pd(II) is required for the reaction to take place. It is known that $Pd^0(PPh_3)_4$ can form the corresponding bis(triphenylphosphine)oxygenopalladium(II) and triphenylphosphine oxide by reacting with molecular oxygen (Scheme 4).[14]

Here the Pd(0) catalyst is first oxidized to the oxygenopalladium(II) intermediate that next can be converted to a Pd(II) species via protonation and H_2O_2 generation.[6a,17] Along the formation of $(PPh_3)_2Pd^{II}O_2$ an intermediate $Pd^0(PPh_3)_2$ species is first formed (Scheme 4) together with triphenylphosphine oxide. It is also possible that the bis-ligated $Pd^0(PPh_3)_2$ could act as a catalyst, while molecular oxygen facilitates the dissociation of two phosphine ligands by oxidizing them. It is in fact known that the dissociation of two or more triphenylphosphine ligands from $Pd^0(PPh_3)_4$ is an endergonic process.[15] It should be considered, however, that bis-ligated Pd(0) species are very easily oxidized to Pd(II) species.[14,16] It is therefore reasonable to assume that, in the presence of molecular oxygen, both Pd(0) and Pd(II) species could be present in the reaction mixture. In order to further investigate these possibilities, we designed another set of experiments. We first synthesized $Pd^{II}(PPh_3)_2O_2$ according to the literature procedure and used it as the cocatalyst for the reaction between **1a** and **2a** in the presence of amine **5a** (Figure 1b, trace F). We observed a dramatic rate acceleration in comparison to the employment of $Pd^0(PPh_3)_4$ as catalyst (trace A, Figure 1a) and no lag time. We also carried out the same transformation using $Pd^{II}(PPh_3)_2O_2$ as the starting catalytic species under an inert atmosphere, and we observed rapid immediate carbocyclization product **4a** formation (Figure 1b, trace G). Thus, this indicates that the carbocyclization transformation where Pd(0) is converted to the active catalytic Pd(II) species via the oxygenopalladium(II) species $Pd^{II}(PPh_3)_2O_2$ is a viable route.[6a,17] The generation of hydrogen peroxide from these type of complexes is known[14,17b] as well as possible disproportionation.[17a] We also tested the commercially available $Pd^0[P(o\text{-tolyl})_3]_2$ as the cocatalyst for the reaction between **1a** and **2a** in the presence of amine **5a** (Figure 1b, trace H). A dramatic rate acceleration in comparison to that for the employment of $Pd^0(PPh_3)_4$ as catalyst (trace A, Figure 1a) was observed without a lag time. This was also the case when

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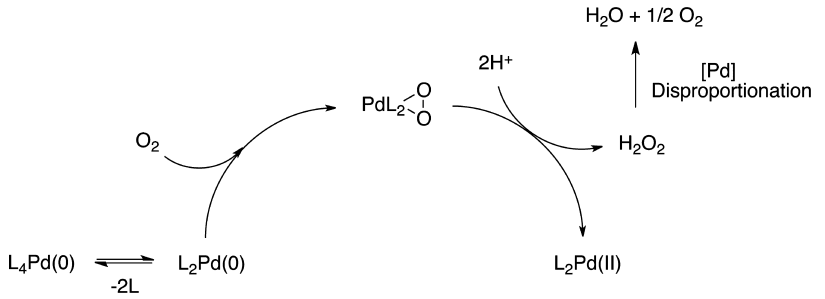
Scheme 4. Oxidation of Pd(0) to Pd(II) by Molecular Oxygen[a]



[a]L = PPh_3.

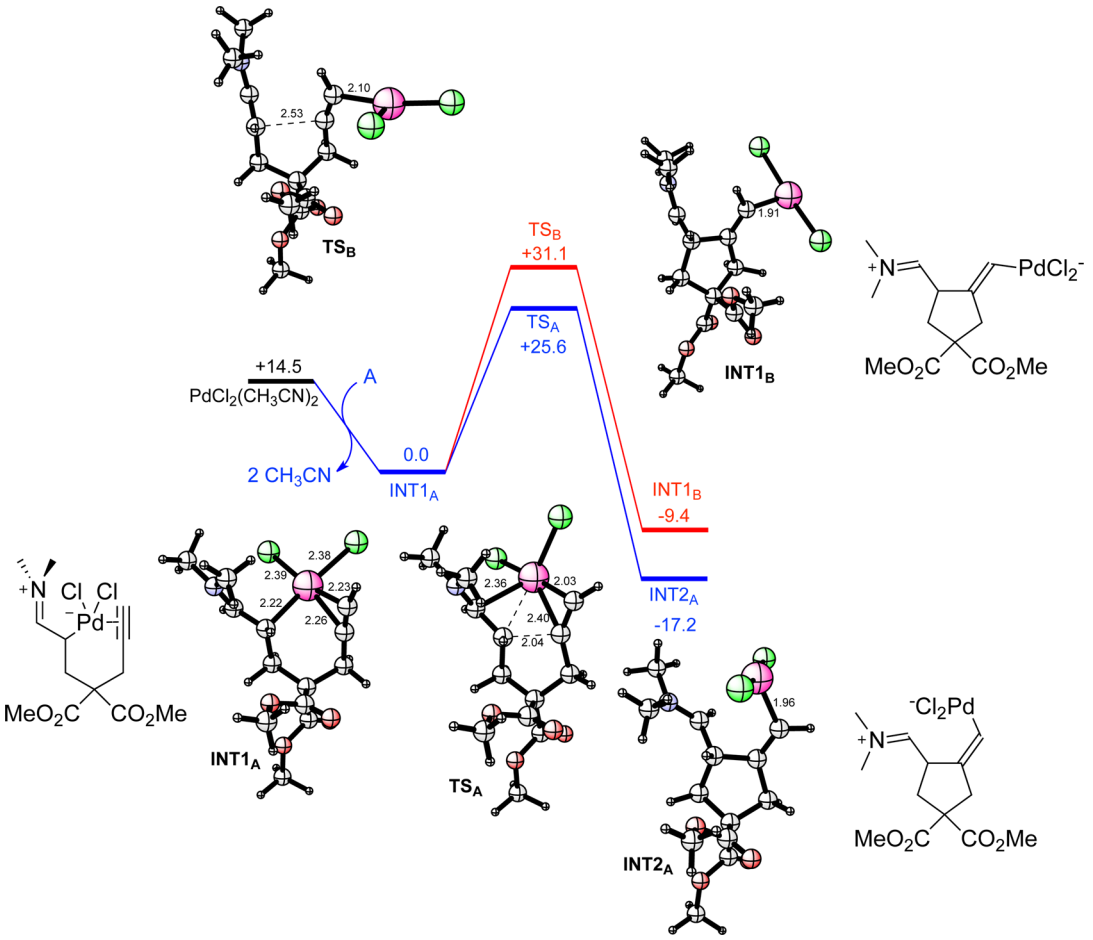


Figure 2. Free energy profile and optimized structures for the $Pd^{II}Cl_2$-catalyzed carbocyclization. Energies are given in kcal/mol and distances in ångströms.

the reaction was performed under an inert atmosphere, and rapid immediate carbocyclization product **4a** formation was observed (Figure 1b, trace I). This could indicate that a bis-ligated Pd(0) species is a competent catalyst for C−C bond formation. However, due to the high sensitivity of bis-ligated Pd(0) species toward oxidation, it cannot be excluded that, even under the inert conditions of the current experiments, some Pd(0) is oxidized to Pd(II), with the latter being responsible for the catalysis.

We also performed high-resolution mass spectral (HRMS) analysis on the crude reaction mixture of the $Pd^0(PPh_3)_4$ and **5a** cocatalyzed transformation.[18] The HRMS analysis confirmed the presence of iminium intermediates **I** and **V** and enaminyne intermediate **II** (see Scheme 5). It is noteworthy that O═PPh_3, which is the known side product from the formation of both $Pd(PPh_3)_2O_2$ and $Pd^0(PPh_3)_2$ (see above), was also detected. Moreover, we followed the $Pd^0(PPh_3)_4$ and **5a** cocatalyzed reaction using ^{31}P NMR and ^1H NMR analysis. The experiments revealed that carbocyclization to **4a** only occurred when O═PPh_3 was produced. Otherwise, only the Michael intermediates **3** were detected by the ^1H NMR analysis.

The above results thus demonstrate that the carbocyclization reaction of enaminynes can be catalyzed by Pd(II) species. When $Pd^0(PPh_3)_4$ is used as the cocatalyst, it has first to be converted by molecular oxygen to another catalytically active

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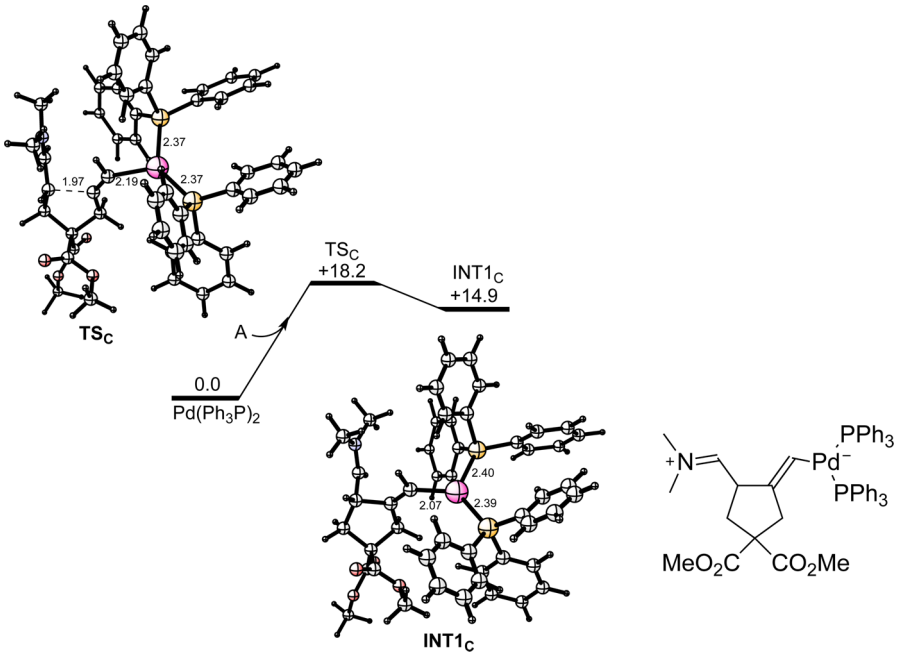

Figure 3. Free energy profile and optimized structures for the $Pd^0(PPh_3)_2$-catalyzed carbocyclization.

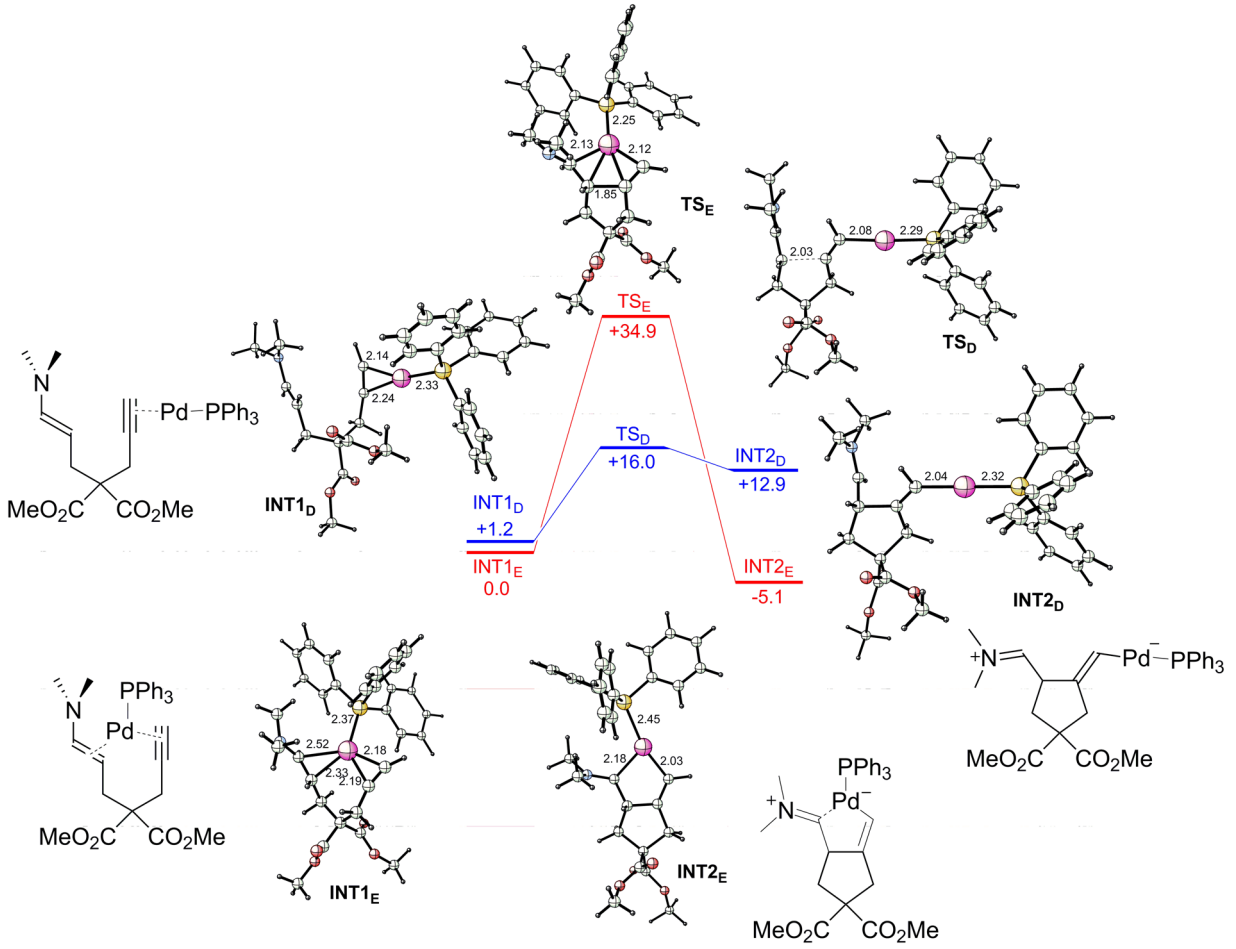

Figure 4. Free energy profile and optimized structures for the $Pd^0(PPh_3)$-catalyzed carbocyclization.

species, with the oxidation of the metal to Pd(II) as a likely scenario. We also investigated the presence of nonlinear effects[19] for the catalytic reaction between **1a** and **2a** using $Pd^0(PPh_3)_4$ and **5a** as cocatalysts (eq 1). A linear relationship between the ee of **5a** and that of product **4a** was observed (see the Supporting Information), thus corroborating the presence

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of one Pd catalyst molecule and one chiral amine **5a** molecule in the transition state.[19] Furthermore, this result, the results from the HRMS analyses, and the high measured enantiomeric excess of product **4a** reveal that chiral amine **5a** has formed the enaminyne intermediate **II**, which interacts with an achiral Pd complex species during the C−C bond-forming transition state.

Theoretical Studies. To shed more light on the mechanism of the Pd-catalyzed cyclization, we performed DFT calculations on the carbon−carbon bond-forming step. We modeled enamine **A**, derived from the condensation of dimethyl 2-(3-oxopropyl)-2-(prop-2-yn-1-yl)malonate with dimethylamine, as the reactant. We first modeled the reaction using $Pd^{II}Cl_2$ as the cocatalyst, since it proved to be active in the experiments (see above) and it also represents a general model for Pd(II) catalysts (Figure 2). Two possible pathways were considered: either (1) the palladium coordinating to both the enamine and the alkyne to afford the product of a syn-carbopalladation of the alkyne (pathway A) or (2) the Pd(II) salt acting as a Lewis acid to afford the product of an anti-carbopalladation (pathway B). The barrier for the first process was found to be the most reasonable (25.6 kcal/mol), while pathway B has a barrier of 31.1 kcal/mol (see Figure 2). Importantly, the C−C bond-forming step of pathway A was calculated to be exergonic by 17.2 kcal/mol. Interestingly, the reaction occurring through pathway A can be described as a two-step process. In the first step, the formation of $\mathbf{INT1_A}$, the $PdCl_2$ coordinates to the alkyne and the enamine. An analysis of the geometries shows that at $\mathbf{INT1_A}$ a nucleophilic attack by the enamine on Pd has occurred. In $\mathbf{INT1_A}$ the palladium is much closer to the β-carbon of the iminium than to the α-carbon (2.22 vs 2.80 Å), the nitrogen geometry is almost planar, and the β-carbon has essentially a tetrahedral geometry. In the second step ($\mathbf{TS_A}$) the C−C bond formation occurs through a Heck-like insertion on the alkyne, leading to the cyclopalladation intermediate $\mathbf{INT2_A}$.

These results confirm that Pd(II) can catalyze the carbon−carbon bond formation. In fact, the Pd(II)-catalyzed reaction according to pathway A has a reasonable barrier, is exergonic, and affords the expected carbocyclization intermediate. Here, it should be mentioned that we also modeled the Pd(II)-catalyzed carbocyclization of the enaminyne derived from the condensation between 3-(prop-2-yn-1-yloxy)propanal and dimethylamine. The results were very analogous to the case of carbocyclization of enaminyne **A** (see the Supporting Information).

Next, we modeled the possibility of a Pd(0)-catalyzed process. We first considered the reaction with two phosphines coordinating to the Pd(0) catalyst. We located the transition state for the palladium-catalyzed cyclization, with the metal coordinating the alkyne on the opposite side with respect to the enamine attack, so that the carbopalladation of the triple bond occurs in an anti fashion (Figure 3).

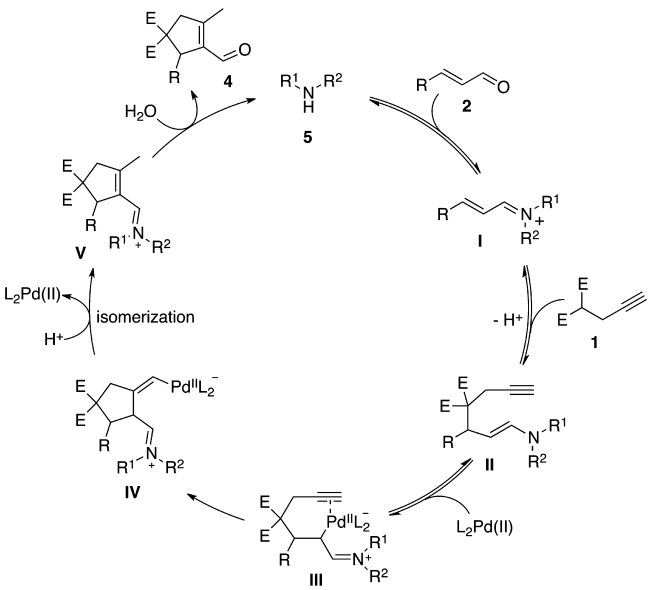
We found the reaction barrier to be reasonable (18.2 kcal/mol), but the reaction step was calculated to be highly endergonic, by 14.9 kcal/mol. As mentioned above, the dissociation of PPh_3 ligands from $Pd(PPh_3)_4$ is known to be an endergonic process. For instance, the dissociation of two ligands necessary to give the bis-ligated catalytic species considered here has been calculated to be endergonic by 12.9 kcal/mol.[15] Normally this value should be added to the calculated barrier, and this would make the overall barrier too high (31.1 kcal/mol) for the cyclization to be feasible through this mechanism. However, as discussed above, oxygen can oxidize phosphines and this can shift the equilibrium toward the formation of lower ligated species when the reaction is performed in the presence of oxygen.

We also considered the possibility of Pd(0) catalyzing the cyclization with only one phosphine ligand coordinated (Figure 4). Two options were found here: either the Pd species acting as a Lewis acid coordinating to the alkyne from the opposite side of the enamine (pathway D) or the Pd species coordinating both to the alkyne and the enamine (pathway E). The latter was calculated to be associated with a high energy barrier (34.9 kcal/mol), while the former (pathway D) has a reasonable barrier of 16.0 kcal/mol. This is of course provided that the oxidation of phosphine ligands can shift the equilibrium toward the formation of the monoligated catalytic species.

The calculations thus suggest that the cyclization through a Pd(0)-catalyzed mechanism would be kinetically feasible. However, the fact that the processes are highly endergonic (Figures 3 and 4), which is in contrast to the highly exergonic $Pd^{II}Cl_2$ catalyzed C−C bond formation (Figure 2), might indicate that the possibility of Pd(0) as the catalyst is less likely, because the barrier for the following step would be added to these values. Since the rest of the catalytic cycles have not been calculated explicitly, a definitive conclusion regarding this issue cannot, however, be drawn solely on the basis of the current calculations.

To summarize the computational part, the DFT calculations confirm that the cyclization step can be catalyzed by Pd(II). When the reaction is catalyzed by $PdCl_2$, here used as a model for Pd(II) catalysts, the process occurs through a nucleophilic attack by the enamine on the alkyne-coordinated palladium, followed by a Heck-like insertion into the alkyne affording the product of syn carbopalladation (Scheme 5). Furthermore, the results suggest that, when the reaction is performed using $Pd(PPh_3)_4$ as cocatalyst, molecular oxygen not only is required to facilitate the ligand dissociation but is also likely to oxidize Pd(0) to Pd(II).

Scheme 5. Proposed Mechanism Based on the Computational and Experimental Results



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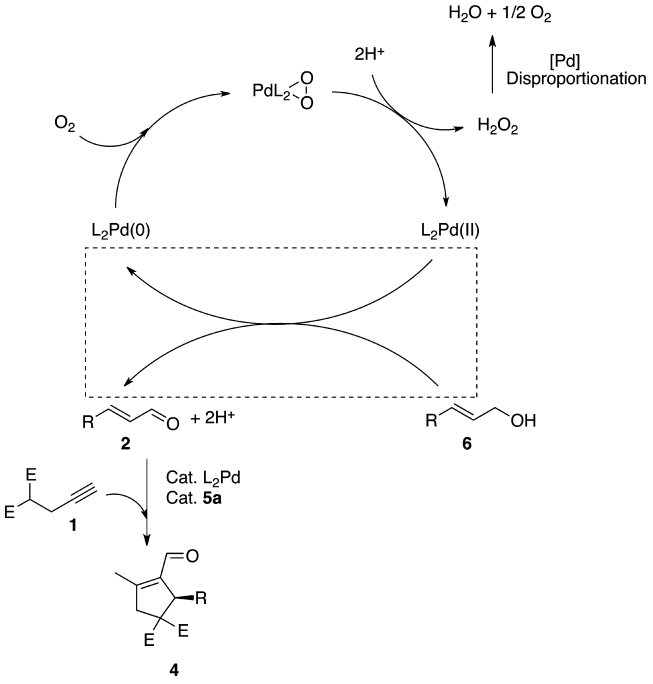
On the basis of this analysis, the most likely catalytic cycle that emerges from the combined experimental/theoretical investigation involves a Pd(II) species as the active catalyst, as shown in Scheme 5. In the initial part of the cycle aldehyde **2** reacts with amine catalyst **5** to form iminium intermediate **I**. Next, a nucleophilic attack of substrate **1** on the β-position of the iminium gives enamine intermediate **II**. After a nucleophilic attack of the enamine on Pd(II) (**II** → **III**) a Heck-like insertion occurs, affording the cyclization intermediate **IV**. Next, protonation and isomerization of **IV** give intermediate **V** and the free Pd(II) species. Finally, the completion of the catalytic cycle requires the hydrolysis of **V** to regenerate catalyst **5** and release product **4**. It should be noted, however, that the participation of a Pd(0) species as the active catalyst cannot be ruled out on the basis of the current results.

Aerobic Allylic Alcohol Oxidation/Michael/Carbocyclization Catalytic Relay. As mentioned above, the development of cascade relay reactions is highly important and is the way Nature assembles its complex biomolecules.[1] In this context, it is noteworthy that our mechanistic findings suggest that it should be possible to merge a Pd(II)/Pd(0) catalyzed aerobic oxidation with the Pd(II)/amine cocatalyzed dynamic Michael/carbocyclization cascade reactions by using allylic alcohols **6** as substrates (Scheme 6), thus linking "Pd-oxidase catalysis" with "metal/organo cooperative catalysis" through completion of the catalytic redox cycle of Pd(II)/Pd(0) and in situ generation of enals **2**. Despite the fact that $Pd^0(PPh_3)_4$ is not the best aerobic oxidation catalyst,[6] we investigated this novel catalysis relay. To our delight, the corresponding carbocycles or spirolactams **4** were isolated as the sole products in good to high yields, drs, and ees using cinnamic alcohols **6**, molecular oxygen, and **1a,b** as the starting substrates and bench-stable $Pd^0(PPh_3)_4$ and amine **5a** as catalysts (Scheme 7). Moreover, we found that allylic alcohols with aliphatic substituents or cinnamic aldehydes with electron-withdrawing groups were poor substrates for the $Pd^0(PPh_3)_4$ catalyzed aerobic oxidations to enals **2** under our conditions. This is in accordance with previous published work on the use of $Pd^0(PPh_3)_4$ as an aerobic oxidation catalyst, as stated above.[6d,f] Furthermore, if hydrogen peroxide is generated as an intermediate in the transformation, it could either replace O_2 as a reoxidant for Pd(0) or react with palladium to generate a reactive oxygen species capable of oxidizing the alcohol substrate.[17] Here we found that hydrogen peroxide (1 equiv) instead of dioxygen converted alcohol **6a** to enal **1a** (98% conversion, 24 h, >98% selectivity) using $Pd^0(PPh_3)_4$ (5 mol %) in toluene at 70 °C. Thus, H_2O_2 was an intermediate during the $Pd^0(PPh_3)_4$ catalyzed transformations with molecular oxygen. Notably, it should also be possible to expand this proof of concept Pd/amine cascade catalysis transformation to other more efficient Pd(0) oxidation catalysts in comparison to $Pd^0(PPh_3)_4$. In this context, the mechanistic work disclosed here led to our recent developments of combined heterogeneous Pd/chiral amine multiple relay catalysis for efficient syntheses of complex organic compounds.[20] Here the Pd(0)−aminopropyl−mesocellular foam (Pd^0-AmP-MCF) or Pd(0)−aminopropyl−controlled pore glass (Pd^0-AmP-CPG) cocatalyzed heterogeneous systems exhibit a wide substrate scope under the same conditions in comparison to the case when $Pd^0(PPh_3)_4$ is used as a homogeneous cocatalyst (Scheme 7).[20]

Scheme 6. Aerobic Allylic Alcohol Oxidation/Michael/Carbocyclization Catalytic Relay



CONCLUSION

In summary, we have investigated the mechanism for the palladium and amine cocatalyzed intermolecular nucleophilic addition of unmodified aldehydes to alkynes. Theory in combination with experiments revealed that this C−C bond-forming transformation is most likely a two-step carbocyclization of enaminynes that is catalyzed by a Pd(II) species. In the first step, the nucleophilic enamine attacks the electrophilic Pd(II), while in the second step an insertion into the alkyne bond affords the carbopalladation intermediate. Very importantly, this cycle was efficiently linked to a highly enantioselective aerobic allylic alcohol oxidation/Michael/carbocyclization catalytic relay using a bench-stable palladium complex and a simple chiral amine. Thus, the current study sets the stage for the merging of "Pd oxidase catalysis" with "metal/organo cooperative catalysis" for application in green and sustainable chemistry. Future research toward this is ongoing in our laboratories and will be disclosed in due time.[20] Here the organocatalysts can interact in synergy with both heterogeneous and homogeneous transition-metal catalyst systems. This excellent ability should also make it a suitable small-molecule catalyst in cooperation with a "cocktail"[21] of metal catalysts in organic synthesis.

EXPERIMENTAL SECTION

Computational Details. All calculations were performed using the B3LYP functional[22] as implemented in the Gaussian03 software package.[23] Geometries were optimized with the LANL2DZ pseudopotential[24] for Pd and the 6-31G(d,p) basis set for the other atoms (BS1) and characterized with frequency calculations. Final energies were obtained with the LANL2DZ pseudopotential for Pd and the larger 6-311+G(2d,2p) basis set on all atoms (BS2) and corrected for zero-point effects and thermal corrections at 298 K obtained from the frequency calculations. The effect of solvation was calculated using the conductor-like polarizable continuum

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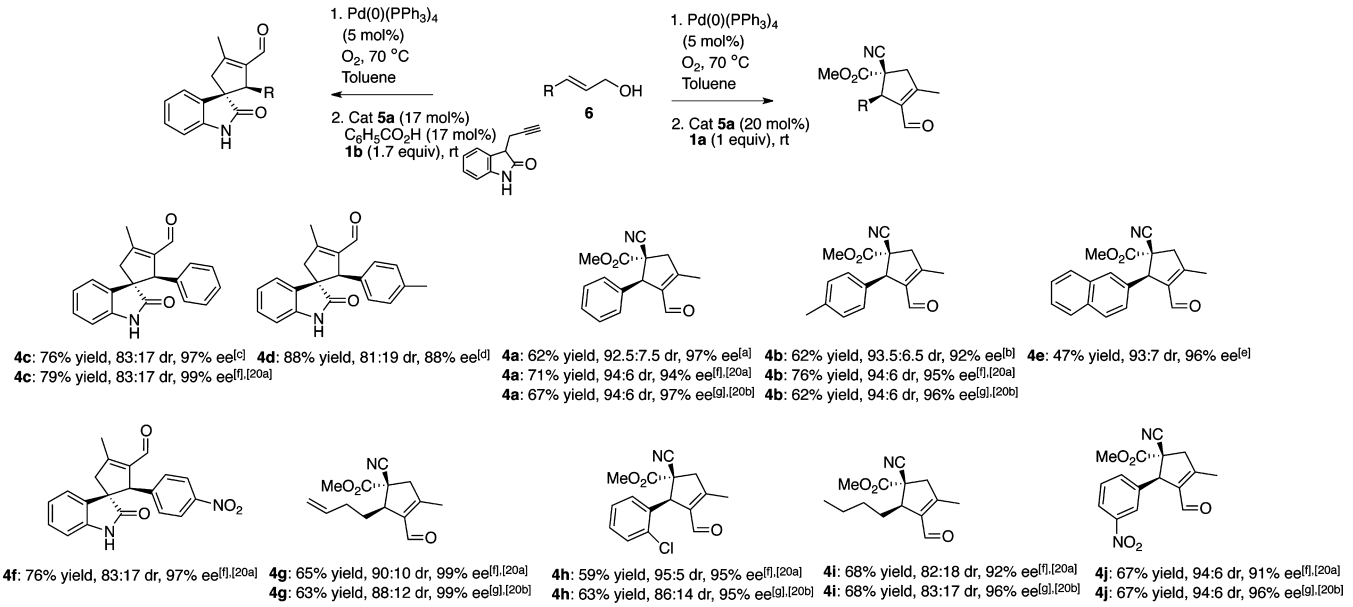
Scheme 7



[a]Conditions: (1) 6 h; (2) 16 h. [b]Conditions: (1) 48 h; (2) 42 h. [c]Conditions: (1) 6 h; (2) 17h. [d]Conditions: (1) 48 h; (2) 21 h. [e]Conditions: (1) 48 h; (2) 23 h. [f]Pd^0-Amp-MCF (5 mol %) was used as the Pd catalyst. See ref 20a. [g]Pd^0-Amp-CPG (5 mol %) was used as the Pd catalyst. See ref 20b.

model (CPCM)[25] with UAKS radii at the B3LYP/BS1 level, with the parameters for either acetonitrile or tetrahydrofuran, depending on the experimental conditions. The energies are also corrected for dispersion effects using the B3LYP-D3 method of Grimme[26] with Becke and Johnson (BJ) damping.[27] Recent reports have shown that inclusion of dispersion effects can significantly improve the performance of the B3LYP method.[28]

Experimental Procedures. *General Considerations.* Chemicals and solvents were either purchased purissimum p.a. from commercial suppliers or purified by standard techniques. The pyrrolidine catalyst **5a** and $Pd(PPh_3)_2O_2$ were synthesized according to literature procedures (see the Supporting Information). For thin-layer chromatography (TLC), Merck 60 F254 silica gel plates were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of ammonium molybdate (100 g), $Ce(SO_4)_2$ (2 g), and 10% H_2SO_4 (1 L) followed by heating or by treatment with a solution of potassium permanganate (3 g), K_2CO_3 (20 g), 5% aqueous NaOH (5 mL), and water (300 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040−0.063 mm), ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker AM400 or Varian AS400 instruments. Chemical shifts are given in δ relative to tetramethylsilane (TMS), and the coupling constants J are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature; TMS served as internal standard (δ 0 ppm) for ^1H NMR, and $CDCl_3$ was used as internal standard (δ 77.16 ppm) for ^{13}C NMR. HPLC was carried out using a Waters 2690 Millenium with photodiode array detector. Optical rotations were recorded on a PerkinElmer 241 Polarimeter (d = 589 nm, 1 dm cell). High-resolution mass spectra (ESI) were obtained with a Bruker MicroTOF spectrometer.

*Carbocyclization between Cinnamic Aldehyde and Methyl 2-Cyanopent-4-ynoate in the Presence of $Pd(PPh_3)_4$ and Chiral Amine **5a**.* To a stirred solution of propargyl malonate **1a** (0.375 mmol, 1 equiv) in CH_3CN (0.6 mL) was added $Pd(PPh_3)_4$ (5 mol %). After the mixture was stirred for 5 min, the chiral pyrrolidine catalyst **5a** (20 mol %) and cinnamic aldehyde **2a** (0.25 mmol, 1 equiv) were added sequentially. The reaction mixture was stirred at room temperature, and the formations of **3a**, **3aa**, and **4a** were measured by placing aliquots (5 μL) of the reaction mixture in NMR vials with $CDCl_3$ (0.6 mL) followed by freezing with liquid nitrogen. Next, ^1H NMR or ^{31}P NMR analysis was performed.

*Carbocyclization between Cinnamic Aldehyde and Methyl 2-Cyanopent-4-ynoate in the Presence of $Pd(PPh_3)_4$ and Chiral Amine **5a** under an Inert Atmosphere.* To a solution of propargyl malonate **1a** (0.375 mmol, 1 equiv) in degassed CH_3CN (0.6 mL) was added $Pd(PPh_3)_4$ (5 mol %) in a glovebox. Next, the chiral pyrrolidine catalyst **5a** (20 mol %) and cinnamic aldehyde **2a** (0.25 mmol, 1 equiv) were added sequentially. The reaction mixture was stirred at room temperature under an inert atmosphere, and the formations of **3a**, **3aa**, and **4a** were measured by placing aliquots (5 μL) of the reaction mixture in NMR vials with $CDCl_3$ (0.6 mL) followed by freezing with liquid nitrogen. Next, ^1H NMR analysis was performed.

*Carbocyclization between Cinnamic Aldehyde and Methyl 2-Cyanopent-4-ynoate in the Presence of $Pd(PPh_3)_4$, Which Has Been Prestirred in Solution for 2 h under an Oxygen Atmosphere, and Chiral Amine **5a**.* A mixture of $Pd(PPh_3)_4$ in CH_3CN (0.6 mL) was stirred for 2 h in the presence of molecular oxygen. Next, the oxygen balloon was removed and propargyl malonate **1a** (0.375 mmol, 1 equiv), the chiral pyrrolidine catalyst **5a** (20 mol %), and cinnamic aldehyde **2a** (0.25 mmol, 1 equiv) were added sequentially. The reaction mixture was stirred at room temperature, and the formations of **3a**, **3aa**, and **4a** were measured by placing aliquots (5 μL) of the reaction mixture in NMR vials with $CDCl_3$ (0.6 mL) followed by freezing with liquid nitrogen. Next, ^1H NMR analysis was performed.

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Carbocyclization between Cinnamic Aldehyde and Methyl 2-Cyanopent-4-ynoate in the Presence of $Pd(PPh_3)_2O_2$ and Chiral Amine ***5a****.* To a stirred solution of propargyl malonate **1a** (0.375 mmol, 1 equiv) in CH_3CN (0.6 mL) was added $Pd(PPh_3)_4O_2$ (5 mol %). After the mixture was stirred for 5 min, the chiral pyrrolidine catalyst **5a** (20 mol %) and cinnamic aldehyde **2a** (0.25 mmol, 1 equiv) were added sequentially. The reaction mixture was stirred at room temperature, and the formations of **3a**, **3aa**, and **4a** were measured by placing aliquots (5 μL) of the reaction mixture in NMR vials with $CDCl_3$ (0.6 mL) followed by freezing with liquid nitrogen. Next, ^{1}H NMR analysis was performed.

Carbocyclization between Cinnamic Aldehyde and Methyl 2-Cyanopent-4-ynoate in the Presence of $PdCl_2$ and Chiral Amine ***5a****.* A mixture of $PdCl_2$ in CH_2Cl_2 (0.6 mL) was stirred for 5 min. Next, the propargyl malonate **1a** (0.375 mmol, 1 equiv), the chiral pyrrolidine catalyst **5a** (20 mol %), and cinnamic aldehyde **2a** (0.25 mmol, 1 equiv) were added sequentially. The reaction mixture was stirred at room temperature, and the formations of **3a**, **3aa** and **4a** were measured by placing aliquots (5 μL) of the reaction mixture in NMR vials with $CDCl_3$ (0.6 mL) followed by freezing with liquid nitrogen. Next, ^{1}H NMR analysis was performed.

Carbocyclization between Cinnamic Aldehyde and Methyl 2-Cyanopent-4-ynoate in the Presence of $PdCl_2$ and Chiral Amine ***5a*** *in CH_3CN.* A mixture of $PdCl_2$ in CH_3CN (0.6 mL) was stirred for 5 min. Next, the propargyl malonate **1a** (0.375 mmol, 1 equiv), the chiral pyrrolidine catalyst **5a** (20 mol %), and cinnamic aldehyde **2a** (0.25 mmol, 1 equiv) were added sequentially. The reaction mixture was stirred at room temperature, and the formations of **3a**, **3aa** and **4a** were measured by placing aliquots (5 μL) of the reaction mixture in NMR vials with $CDCl_3$ (0.6 mL) followed by freezing with liquid nitrogen. Next, ^{1}H NMR analysis was performed.

Carbocyclization between Cinnamic Aldehyde and Methyl 2-Cyanopent-4-ynoate in the Presence of $Pd(PPh_3)_2O_2$ and Chiral Amine ***5a*** *under an Inert Atmosphere.* To a solution of propargyl malonate **1a** (0.375 mmol, 1 equiv) in degassed CH_3CN (0.6 mL) was added $Pd(PPh_3)_2O_2$ (5 mol %) in a glovebox. Next, the chiral pyrrolidine catalyst **5a** (20 mol %) and cinnamic aldehyde **2a** (0.25 mmol, 1 equiv) were added sequentially. The reaction mixture was stirred at room temperature under an inert atmosphere, and the formations of **3a**, **3aa**, and **4a** were measured by placing aliquots (5 μL) of the reaction mixture in NMR vials with $CDCl_3$ (0.6 mL) followed by freezing with liquid nitrogen. Next, an ^{1}H NMR analysis was performed.

Carbocyclization between Cinnamic Aldehyde and Methyl 2-Cyanopent-4-ynoate in the Presence of $PdCl_2$ and Chiral Amine ***5a*** *under an Inert Atmosphere.* To a solution of propargyl malonate **1a** (0.375 mmol, 1 equiv) in degassed CH_3CN (0.6 mL) was added $PdCl_2$ (5 mol %) in a glovebox. Next, the chiral pyrrolidine catalyst **5a** (20 mol %) and cinnamic aldehyde **2a** (0.25 mmol, 1 equiv) were added sequentially. The reaction mixture was stirred at room temperature under an inert atmosphere and the formations of **3a**, **3aa** and **4a** were measured by placing aliquots (5 μL) of the reaction mixture in NMR vials with $CDCl_3$ (0.6 mL) followed by freezing with liquid nitrogen. Next, ^{1}H NMR analysis was performed.

Aerobic Allylic Alcohol Oxidation/Michael/Carbocyclization Catalytic Relay to ***4a****.* Cinnamic alcohol (0.24 mmol, 1.2 equiv) and $Pd(PPh_3)_4$ (5 mol % to **1a**, 11.5 mg) were weighed into a microwave vial and suspended in toluene (0.5 mL). The vial was capped and evacuated, and an oxygen balloon was connected to the reaction vessel. The reaction mixture was stirred at 70 °C for 6 h. Next, the reaction mixture was cooled to room temperature and propargyl malonate **1a** (0.2 mmol, 1 equiv) and catalyst **5a** (20 mol %, 13 mg) were added sequentially. After it was stirred vigorously for 16 h, the crude reaction mixture was directly loaded on a silica gel column and the next chromatograph (3/1 pentane/EtOAc mixture) afforded the corresponding product **5a** (34 mg, 62% yield).

*(1R,2R)-Methyl 1-Cyano-3-formyl-4-methyl-2-phenylcyclopent-3-enecarboxylate (****4a****).* Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (s, 1H), 7.38−7.32 (m, 3H), 7.17−7.15 (m, 2H), 4.72 (bs, 1H), 3.88 (s, 3H), 3.41 (d, J = 14.8 Hz, 1H), 3.26 (d, J = 14.8 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 186.2, 168.8, 157.9, 136.8, 136.6, 129.0, 128.7, 128.0, 117.4, 58.4, 54.4, 51.7, 47.8, 14.3. HRMS (ESI): calcd for [M + Na] ($C_{16}H_{15}NO_3$) m/z 292.0944, found 292.0944. $[\alpha]_D^{25}$ = −5.2° (c 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH column, n-hexane/i-PrOH 85/15, λ 210 nm, 1.0 mL/min): t_r (major enantiomer) = 17.0 min, t_r (minor enantiomer) = 27.0 min.

*(1R,2R)-Methyl 1-Cyano-3-formyl-4-methyl-2-(p-tolyl)-cyclopent-3-enecarboxylate (****4b****).* Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.16 (d, J = 6.4 Hz, 2H), 7.04 (d, J = 6.4 Hz, 2H), 4.68 (bs, 1H), 3.88 (s, 3H), 3.39 (d, J = 14.8 Hz, 1H), 3.25 (d, J = 14.8 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 186.3, 168.9, 157.7, 138.4, 136.8, 133.6, 129.8, 127.9, 117.6, 58.2, 54.4, 51.8, 47.8, 21.4, 14.3. HRMS (ESI): calcd for [M + Na] ($C_{17}H_{17}NO_3$) m/z 306.1101, found 306.1104. $[\alpha]_D^{25}$ = −81.6° (c = 1.3, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH column, n-hexane/i-PrOH 90/10, λ 250 nm, 1.0 mL/min): t_r (major enantiomer) = 23.9 min, t_r (minor enantiomer) = 32.9 min.

*(1R,2R)-Methyl 1-Cyano-3-formyl-4-methyl-2-(naphthalen-2-yl)cyclopent-3-enecarboxylate (****4d****).* oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H), 7.87−7.80 (m, 3h), 7.16 (d, J = 1.2 Hz, 1H), 7.50−7.45 (m, 2H), 7.28 (dd, J = 2.0 Hz, $\acute{J}$ = 6.4 Hz, 1H), 4.90 (bs, 1H), 3.90 (s, 3H), 3.38 (q, J = 18.8 Hz, $\acute{J}$ = 26.0 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 186.2, 168.9, 158.0, 136.8, 134.1, 133.5, 133.5, 128.9, 128.2, 127.9, 127.3, 126.4, 126.4, 125.7, 117.4, 58.5, 54.5, 51.7, 48.0, 14.4. HRMS (ESI): calcd for [M + Na] ($C_{20}H_{17}NO_3$) m/z 342.1101, found 342.1098. $[\alpha]_D^{25}$ = −127.5° (c = 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH column, n-hexane/i-PrOH 70/30, λ 230 nm, 1.0 mL/min): t_r (major enantiomer) = 13.2 min, t_r (minor enantiomer) = 30.9 min.

Aerobic Allylic Alcohol Oxidation/Michael/Carbocyclization Catalytic Relay to ***4c****.* Cinnamic alcohol (0.24 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (5 mmol %, 14 mg) were weighed into a microwave vial and suspended in toluene (0.5 mL). The vial was capped and evacuated, and an oxygen balloon was connected to the reaction vessel. The reaction mixturewas stirred at 70 °C for 6 h. Then the reaction mixture was cooled to room temperature and toluene (0.5 mL), propargyl-2-oxindole **1b** (0.4 mmol, 1.7 equiv), catalyst **5a** (17 mol %, 13 mg), and benzoic acid (17 mol %, 5 mg) were added sequentially. After vigorous stirring for 20 h, the crude reaction mixture was directly loaded on a silica gel column and an

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immediate chromatograph (pentane/EtOAc) afforded the corresponding product **4c** (55 mg, 76% yield).

*(1R,2R)-4-Methyl-2′-oxo-2-phenylspiro[cyclopent[3]ene-1,3′-indoline]-3-carbaldehyde (**4c**).* Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (s, 1H), 8.26 (bs, 1H), 7.11−7.10 (m, 3H), 7.03−6.99 (m, 1H), 6.84−6.82 (m, 2H,), 6.73 (d, J = 8.0 Hz, 1H), 6.63 (t, J = 0.8 Hz, 1H), 6.24 (d, J = 7.6 Hz, 1H), 4.63 (bs, 1H), 3.0 (dd, J = 18.8 Hz, J = 18.4 Hz, 2H), 2.42 (d, J = 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 187.3, 182.7, 160.9, 140.3, 138.1, 137.8, 130.6, 128.2, 128.0, 127.3, 125.1, 122.0, 109.4, 58.4, 56.6, 49.0, 14.9. HRMS (ESI): calcd for [M + Na] ($C_{20}H_{17}NO_2$) m/z 326.1151, found 326.1154. $[\alpha]_D^{25}$ = −70.3° (c = 1, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH column, n-hexane/i-PrOH 80/20, λ 254 nm, 1.0 mL/min): t_r (major enantiomer) = 29.5 min, t_r (minor enantiomer) = 20.8 min.

*(1R,2R)-4-Methyl-2′-oxo-2-(p-tolyl)spiro[cyclopent[3]ene-1,3′-indoline]-3-carbaldehyde (**4d**).* ^{1}H NMR (400 MHz, $CDCl_3$):δ 10.06 (s, 1H), 8.10 (bs, 1H), 7.04 (t, J = 1.2 Hz, 1H), 6.91 (d, J = 8.0 Hz, 2H), 6.75−6.70 (m, 3H), 6.63 (t, J = 7.6 Hz, 1H), 6.43 (d, J = 7.6 Hz, 1H), 4.59 (bs, 1H), 2.98 (q, J = 18.4 Hz, J= 15.2 Hz, 2H), 2.41 (d, J = 1.6 Hz, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 187.4, 182.6, 160.6, 140.3, 138.0, 136.8, 135.0, 130.7, 128.9, 128.1, 128.0, 125.2, 122.0, 109.4, 58.0, 56.6, 49.0, 21.2, 15.0. HRMS (ESI): calcd for [M + Na] ($C_{21}H_{19}NO_2$) m/z 340.1308, found 340.1310. $[\alpha]_D^{25}$ = −120.4° (c = 1, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH column, n-hexane/i-PrOH 80/20, λ 250 nm, 1.0 mL/min): t_r (major enantiomer) = 39.2 min, t_r (minor enantiomer) = 19.5 min.

HRMS Spectral Analysis of the Crude Reaction Mixture. To a stirred solution of propargyl malonate **1a** (0.375 mmol, 1 equiv) in CH_3CN (0.6 mL) was added $Pd(PPh_3)_4$ (5 mol %). After the mixture was stirred for 5 min, the chiral pyrrolidine catalyst **5a** (20 mol %) and cinnamic aldehyde **2a** (0.25 mmol, 1 equiv) were added sequentially. The reaction mixture was stirred at room temperature, and the reaction intermediates were monitored by HRMS by taking aliquots (5 μL) of the reaction mixture that were directly injected into the mass spectrometer.

■ ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs500905r.

Experimental details, computational data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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