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 enamimines 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, multication, 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 multienzyme 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 catalyzed conjugate additions of propargyl nucleophiles to enals 1 and 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,9b dihydrofurans,9b dihydropyrrolidines,9b spirolactams10). 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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In our initial studies of the Pd(0)-catalyzed carbocyclization of aldehyde-derived enamynes, 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). 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. 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. Thus, with
respects 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 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 Pd(0)(PPh3)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)(PPh3)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)(PPh3)4 catalyst at ambient temperature under an oxygen atmosphere for 2 h prior to adding 1a, 2a, and amine cocatalyst 5a resulted in immediate cyclopentene 4a formation (trace C, Figure 1a). The Pd(II)Cl2-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(II)(PPh3)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(II)(PPh3)4 can form the corresponding bis(triphenylphosphine)oxygenopalladium(II) and triphenylphosphine oxide by reacting with molecular oxygen (Scheme 4).

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 H2O2 generation. Along the formation of (PPh3)2PdO2 an intermediate Pd(II)(PPh3)2 species is first formed (Scheme 4) together with triphenylphosphine oxide. It is also possible that the bis-ligated Pd(II)(PPh3)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(II)(PPh3)4 is an endergonic process. It should be considered, however, that bis-ligated Pd(0) species are very easily oxidized to Pd(II) species. 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)(PPh3)2O2 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(II)(PPh3)4 as catalyst (trace A, Figure 1a) and no lag time. We also carried out the same transformation using Pd(II)(PPh3)2O2 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)(PPh3)2O2 is a viable route. The generation of hydrogen peroxide from these type of complex is known as well as possible disproportionation. We also tested the commercially available Pd(II)(PPh3)2O2, 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(II)(PPh3)4 as catalyst (trace A, Figure 1a) was observed without a lag time. This was also the case when
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 Pd0(PPh3)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==PPh3, which is the known side product from the formation of both Pd(PPh3)2O2 and Pd0(PPh3)2 (see above), was also detected. Moreover, we followed the Pd0(PPh3)4 and 5a cocatalyzed reaction using 31P NMR and 1H NMR analysis. The experiments revealed that carbocyclization to 4a only occurred when O==PPh3 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 enamynes can be catalyzed by Pd(II) species. When Pd0(PPh3)4 is used as the cocatalyst, it has first to be converted by molecular oxygen to another catalytically active
species, with the oxidation of the metal to Pd(II) as a likely scenario. We also investigated the presence of nonlinear effects\textsuperscript{19} for the catalytic reaction between 1a and 2a using Pd\textsuperscript{0}(PPh\textsubscript{3})\textsubscript{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...
of one Pd catalyst molecule and one chiral amine 5a molecule in the transition state.\textsuperscript{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\textsubscript{II}Cl\textsubscript{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 INT1\textsubscript{A} the PdCl\textsubscript{2} coordinates to the alkyne and the enamine. An analysis of the geometries shows that at INT1\textsubscript{A} a nucleophilic attack by the enamine on Pd has occurred. In INT1\textsubscript{A} the palladium is much closer to the \textbeta-carbon of the iminium than to the \textalpha-carbon (2.22 vs 2.80 Å), the nitrogen geometry is almost planar, and the \textbeta-carbon has essentially a tetrahedral geometry. In the second step (TS\textsubscript{A}) the C–C bond formation occurs through a Heck-like insertion on the alkyne, leading to the cyclopalladation intermediate INT2\textsubscript{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-yl)oxy]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\textsubscript{3} ligands from Pd(PPh\textsubscript{3})\textsubscript{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.\textsuperscript{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\textsubscript{II}Cl\textsubscript{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\textsubscript{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\textsubscript{3})\textsubscript{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**
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. 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/organocatalyst" through completion of the catalytic redox cycle of Pd(II)/Pd(0) and in situ generation of enals 2. Despite the fact that Pd(II) is not the best aerobic oxidation catalyst, 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 aldehydes 6, molecular oxygen, and 1a,b as the starting substrates and bench-stable Pd(II) 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(II) catalyzed aerobic oxidations to enals 2 under our conditions. This is in accordance with previous published work on the use of Pd(II) as an aerobic oxidation catalyst, as stated above.

Furthermore, if hydrogen peroxide is generated as an intermediate in the transformation, it could either replace O2 as a reoxidant for Pd(0) or react with palladium to generate a reactive oxygen species capable of oxidizing the alcohol substrate. 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(II) (5 mol %) in toluene at 70 °C. Thus, H2O2 was an intermediate during the Pd(II) 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(II). 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. Here the Pd(0)—aminopropyl—mesocellular foam (Pd0-AmP-MCF) or Pd(0)—aminopropyl—controlled pore glass (Pd0-AmP-CPG) cocatalyzed heterogeneous systems exhibit a wide substrate scope under the same conditions in comparison to the case when Pd(II) is used as a homogeneous cocatalyst (Scheme 7).

**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 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 oxidation catalysis" with "metal/organocatalyst" for application in green and sustainable chemistry. Future research toward this is ongoing in our laboratories and will be disclosed in due time. 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" of metal catalysts in organic synthesis.

**EXPERIMENTAL SECTION**

**Computational Details.** All calculations were performed using the B3LYP functional as implemented in the Gaussian03 software package. Geometries were optimized with the LANL2DZ pseudopotential 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...
model (CPCM)\textsuperscript{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\textsuperscript{26} with Becke and Johnson (BJ) damping.\textsuperscript{27} Recent reports have shown that inclusion of dispersion effects can significantly improve the performance of the B3LYP method.\textsuperscript{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\textsubscript{3})\textsubscript{2}O\textsubscript{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\textsubscript{4})\textsubscript{2} (2 g), and 10% H\textsubscript{2}SO\textsubscript{4} (1 L) followed by heating or by treatment with a solution of potassium permanganate (3 g), K\textsubscript{2}CO\textsubscript{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), \textsuperscript{1}H, \textsuperscript{13}C, and \textsuperscript{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 CD\textsubscript{3}CN as solvent at room temperature; TMS served as internal standard (δ 0 ppm) for \textsuperscript{1}H NMR, and CDCl\textsubscript{3} was used as internal standard (δ 7.26 ppm) for \textsuperscript{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\textsubscript{3})\textsubscript{4} and Chiral Amine 5a.** To a stirred solution of propargyl malonate 1a (0.375 mmol, 1 equiv) in CH\textsubscript{3}CN (0.6 mL) was added Pd(PPh\textsubscript{3})\textsubscript{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\textsubscript{3} (0.6 mL) followed by freezing with liquid nitrogen. Then, \textsuperscript{1}H NMR or \textsuperscript{31}P NMR analysis was performed.

**Carbocyclization between Cinnamic Aldehyde and Methyl 2-Cyanopent-4-ynoate in the Presence of Pd(PPh\textsubscript{3})\textsubscript{4} and Chiral Amine 5a under an Inert Atmosphere.** To a solution of propargyl malonate 1a (0.375 mmol, 1 equiv) in degassed CH\textsubscript{3}CN (0.6 mL) was added Pd(PPh\textsubscript{3})\textsubscript{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\textsubscript{3} (0.6 mL) followed by freezing with liquid nitrogen. Next, \textsuperscript{1}H NMR analysis was performed.

**Carbocyclization between Cinnamic Aldehyde and Methyl 2-Cyanopent-4-ynoate in the Presence of Pd(PPh\textsubscript{3})\textsubscript{4}, Which Has Been Prestirred in Solution for 2 h under an Oxygen Atmosphere, and Chiral Amine 5a.** A mixture of Pd(PPh\textsubscript{3})\textsubscript{4} in CH\textsubscript{3}CN (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\textsubscript{3} (0.6 mL) followed by freezing with liquid nitrogen. Next, \textsuperscript{1}H NMR analysis was performed.
Carbocyclization between Cinnamic Aldehyde and Methyl 2-Cyanopent-4-ynoate in the Presence of Pd(PPh₃)₂O₂ and Chiral Amine 5a. A mixture of PdCl₂ in CH₂Cl₂ (0.6 mL) was stirred for 5 min. Next, the propargyl malonate 1a (0.375 mmol, 1 equiv) 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 CDCl₃ (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 PdCl₂ and Chiral Amine 5a in CH₃CN. A mixture of PdCl₂ in CH₃CN (0.6 mL) was added Pd(PPh₃)₂O₂ (5 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 CDCl₃ (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 PdCl₂ and Chiral Amine 5a under an Inert Atmosphere. To a solution of propargyl malonate 1a (0.375 mmol, 1 equiv) in degassed CH₃CN (0.6 mL) was added Pd(PPh₃)₂O₂ (5 mol %) in a glovebox. Next, the chiral pyrrolidine catalyst 5a (20 mol %) was added and the reaction mixture was directly loaded on a silica gel column and eluted with CHCl₃. The enantiomeric excess was determined by HPLC analysis in comparison with an authentic racemic material (ODH column, n-hexane/i-PrOH 85/15, λ 210 nm, 1.0 mL/min): t₁ (major enantiomer) = 17.0 min, tᵢ (minor enantiomer) = 27.0 min.

(1R,2R)-Methyl 1-Cyano-3-formyl-4-methyl-2-phenylcycloprop-3-ene-carboxylate (4a). A mixture of PdCl₂ in CH₂Cl₂ (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 CDCl₃ (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 PdCl₂ and Chiral Amine 5a under an Inert Atmosphere. To a solution of propargyl malonate 1a (0.375 mmol, 1 equiv) in degassed CH₂CN (0.6 mL) was added Pd(PPh₃)₂O₂ (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 CDCl₃ (0.6 mL) followed by freezing with liquid nitrogen. Next, ¹H NMR analysis was performed.

Aerobic Allylic Alcohol Oxidation/Michael/Carbocyclization Catalytic Relay to 4c. Cinnamic alcohol (0.24 mmol, 1.0 equiv) and Pd(PPh₃)₄ (5 mol %) 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. Then, 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-(p-tolyl)cycloprop-3-ene-carboxylate (4b). A mixture of PdCl₂ in CH₂Cl₂ (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 CDCl₃ (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 PdCl₂ and Chiral Amine 5a in CH₃CN. A mixture of PdCl₂ in CH₃CN (0.6 mL) was stirred for 5 min. Next, the propargyl malonate 1a (0.375 mmol, 1 equiv) 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 CDCl₃ (0.6 mL) followed by freezing with liquid nitrogen. Next, ¹H NMR analysis was performed.
immediate chromatograph (pentane/EtOAc) afforded the corresponding product 4c (55 mg, 76% yield).

(1R,2R)-4-Methyl-2’-oxo-2-phenylsilo[cylocpent[3]ene-1,3’-indoline]-3-carbaldehyde (4d). 1H NMR (400 MHz, CDCl3): 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). 13C NMR (100 MHz, CDCl3): 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, 58.6, 49.0, 21.2, 15.0. HRMS (ESI): calcld for [M + Na] ([C12H15NO2]+) m/z 340.1380, found 340.1310. [α]D 25 = −120.4° (c = 1, CHCl3). 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): tR (minor enantiomer) = 39.2 min, tR (major 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 CH2CN (0.6 mL) was added Pd(PPh3)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 with taking aliquots (5 μL) of the reaction mixture that were directly injected into the mass spectrometer.

**REFERENCES**


