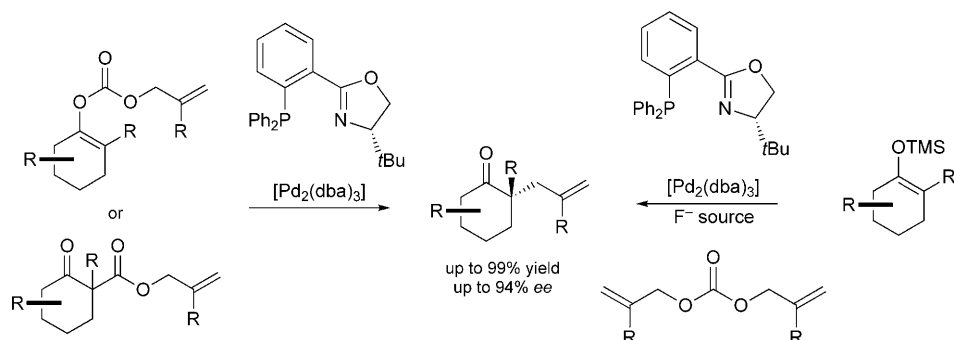


Unusual Allylpalladium Carboxylate Complexes: Identification of the Resting State of Catalytic Enantioselective Decarboxylative Allylic Alkylation Reactions of Ketones**

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We recently developed a series of catalytic enantioselective allylic alkylation reactions of cyclic ketone enolates that proceed by the decarboxylation of allyl carbonates and β -ketoesters (Scheme 1).^[1] These robust reactions proceed in a variety of solvents in the presence of steric hindrance and a wide range of functional groups, and have an unusually high tolerance to water.^[2] To gain further experimental insight into this chemistry, we embarked on a mechanistic study,^[3] which has now resulted in the isolation and full characterization of complex **1** (Figure 1), the resting state of a prototypical reaction. We describe herein the identification of this unusual complex and discuss its potential implications for palladium-catalyzed decarboxylative asymmetric alkylation reactions and other related transformations.

Initially, we sought to follow the catalytic reaction of a standard β -ketoester substrate, ($\pm$)-**2**, by ^{31}P NMR spectroscopy (Figure 2, top). The combination of (*S*)-*t*Bu-phox (**3**) with $[\text{Pd}_2(\text{dba})_3]$ in a 2.6:1 ratio at room temperature for 30 min as specified in our standard alkylation procedure^[1] led to a single new resonance at $\delta = 18.8$ ppm along with the



Scheme 1. Palladium-catalyzed enantioselective decarboxylative allylic alkylation reactions of ketone enolates. dba = *trans,trans*-dibenzylideneacetone, TMS = trimethylsilyl.

signal for the free ligand **3** at $\delta = -5.95$ ppm (Figure 2 A). The addition of β -ketoester ($\pm$)-**2** resulted in the complete disappearance of the resonance at 18.8 ppm and produced a

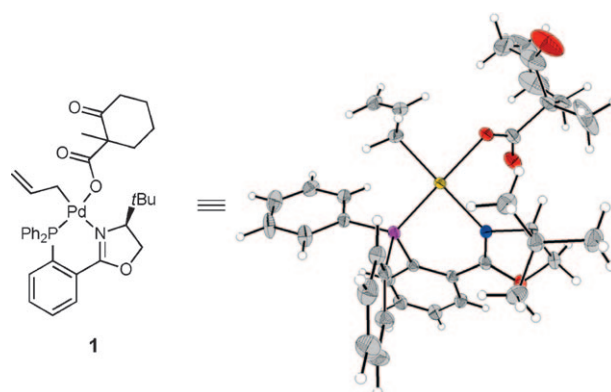


Figure 1. X-ray crystal structure of complex **1** (one diastereomer shown), the resting state of the catalytic cycle. The molecular structure is shown with 50% probability ellipsoids.

long-lived resonance at 30.9 ppm (Figure 2 B). As the reaction to form ketone **4** neared completion, the long-lived intermediate slowly reverted to the initial species with a resonance at 18.8 ppm (Figure 2 C).^[4]

We proceeded to isolate and characterize the complex corresponding to the long-lived resonance at 30.9 ppm and identified it as **1** (Figure 1). Despite the apparent abundance of this complex in solution under the catalytic reaction conditions, **1** proved challenging to isolate owing to its air sensitivity and thermal instability well below 24°C both in solution and as a solvent-free solid.^[5] Interestingly, impure

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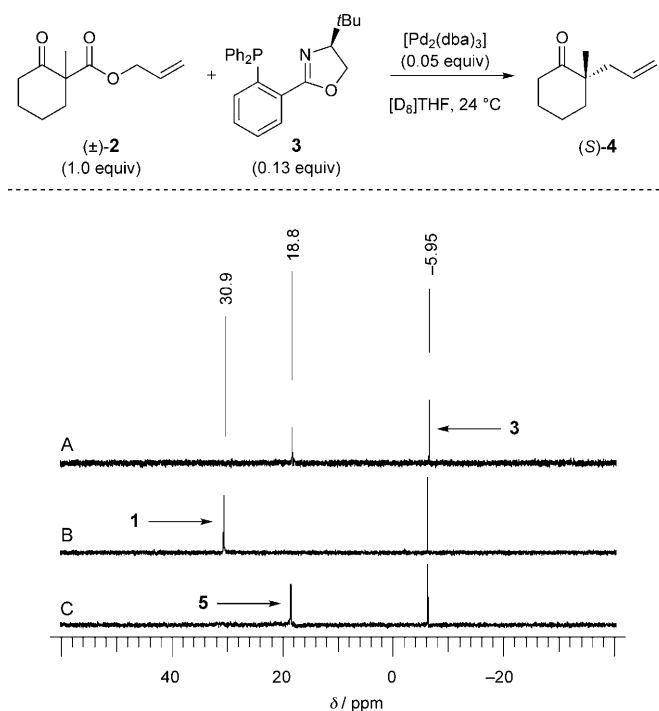


Figure 2. ^{31}P NMR spectroscopic study of the asymmetric allylic alkylation of β -ketoester ($\pm$)-**2**. A) Spectrum of ligand **3** and $[\text{Pd}_2(\text{dba})_3]$ in $[\text{D}_8]\text{THF}$ after 30 min. B) Spectrum after the addition of β -ketoester ($\pm$)-**2** to the above mixture. C) Spectrum after the completion of the reaction to form ketone **4**. Spectra were referenced to 85 % aqueous H_3PO_4 ($\delta = 0.0$ ppm).

samples of **1** visibly expelled a gas (presumably CO_2) in the solid state and effervesced in solvent.^[6] After extensive experimentation, crystals of high purity and reasonable stability were isolated and characterized crystallographically as a mixture of diastereomers resulting from the use of racemic **2**. Complex **1** is a square-planar 16-electron species with a σ -bound, η^1 -allyl ligand *trans* to the nitrogen atom of the phox ligand and a β -ketocarboxylate ligand *trans* to the phosphorus atom. By contrast, the analogous $[(t\text{Bu-phox})\text{Pd}(\eta^3\text{-allyl})]\text{PF}_6$ cationic complex displays η^3 - π -allyl bonding in the solid state,^[3,6,7] as do related structures in solution.^[8]

The structure of intermediate **1** reveals that this complex must form after oxidative addition, but prior to decarboxylation. Because **1** is the only observable species during the course of the catalytic reaction, we concluded that **1** is the catalyst resting state and that the rate-determining step for the allylic alkylation of β -ketoester substrates is decarboxylation.^[4] This result is consistent with our previously reported kinetic data for the overall reaction, which shows a first-order dependence on the catalyst concentration and an apparent zero-order dependence on the substrate concentration.^[3]

The arrangement of the allyl and carboxylate ligands in palladium complex **1** is similar to that previously determined for allyl palladium enolate complex **6** by DFT methods (Figure 3).^[3] Importantly, enolate **6** was described as the penultimate intermediate prior to the key carbon–carbon bond-forming reductive-elimination step in the calculated inner-sphere mechanistic pathway. The high degree of structural similarity between intermediate **1** and complex **6** lends

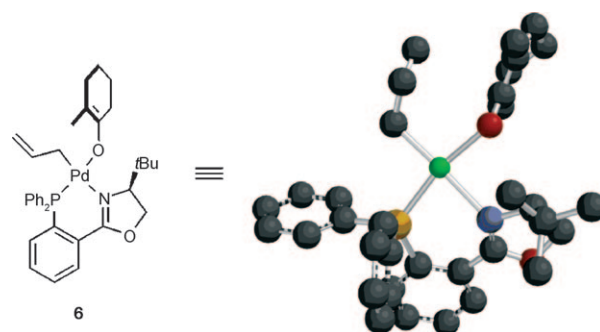


Figure 3. Structure derived from DFT calculations for the intermediate η^1 -allylpalladium enolate prior to C–C bond-forming reductive elimination.^[3] Hydrogen atoms have been removed for clarity.

credence to this key calculated structure, and complex **1** may also represent the best isolable experimental model system for the calculated intermediate.

The crystal structure of intermediate **1** is not only the first example in the Cambridge Structural Database (CCDC 695531) of a palladium species with a β -ketocarboxylate ligand, but it is also the first X-ray crystal structure of a transition-metal complex with a σ -bound allyl group *cis* to a carboxylate ligand.^[9] Given the enormous number of transition-metal-catalyzed reactions involving allylic acetates and carbonates, this structure may have important mechanistic implications not only for immediately related decarboxylative allylic alkylation reactions,^[1,10] but also for palladium-catalyzed allylic oxidation,^[11,12] palladium-catalyzed 1,4-diacetoxylation,^[11,13] and late-transition-metal-catalyzed decarboxylative reactions in general. With this in mind, we synthesized neutral $[(t\text{Bu-phox})\text{Pd}(\eta^1\text{-allyl})(\text{OAc})]$ (**7**) and characterized the complex crystallographically (Figure 4). The structure of complex **7**, a four-coordinate Pd^{II} square-planar species in which the phosphorus atom and the acetate group have a *trans* relationship, is similar to that of carboxylate **1**. Despite its simplicity and central nature to many catalytic pathways, this canonical oxidative-addition adduct of allyl acetate and L_nPd^0 has not been characterized previously.^[14] In light of the availability of η^1 -allyl complexes **1** and **7**, it may be reasonable to consider analogous neutral intermediates in a variety of studies.^[15]

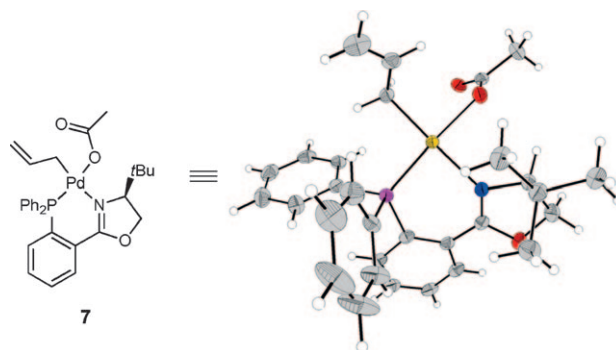
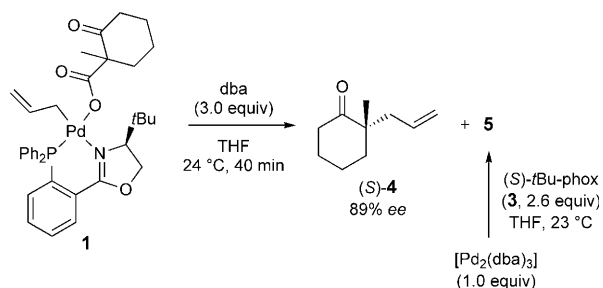


Figure 4. X-ray crystal structure of acetate **7** (one conformation represented). The molecular structure is shown with 50 % probability ellipsoids.

Having identified the resting state of the catalytic cycle, we studied the general reactivity of complex **1**. Samples of intermediate **1** were converted into the allylic alkylation product **4** with 89% *ee* in 40 min in anhydrous THF at 24 °C. This result is consistent with the enantioselectivity observed in catalytic reactions conducted under our standard conditions (Scheme 2).^[1] When this thermal decomposition occurred in the presence of the free dba ligand, complex **5** was generated (Scheme 2).^[16] ³¹P NMR spectroscopy indicated



Scheme 2. Thermal decomposition of complex **1** in the presence of dba, and the independent synthesis of **5**.

that complex **5** was identical to the phosphorus-containing compound observed previously in the ³¹P NMR spectroscopic study described above (Figure 2A,C). Furthermore, complex **5** can be formed independently by mixing [Pd₂(dba)₃] with (S)-*t*Bu-phox (**3**). Thus, complex **5** appears to be the initial adduct in our, and related, allylic alkylation systems,^[10a,b,e] and is the predominant palladium-containing species in the absence of a substrate.

We proceeded to isolate and characterize complex **5**, which was identified by X-ray crystallographic analysis as monomeric [Pd(*t*Bu-phox)(dba)] (Figure 5). Isolated **5** was found to be a competent catalyst for the asymmetric alkylation reaction; the yields and asymmetric induction observed were analogous to those observed with our previously published procedures.^[1,6]

A mechanistic picture for the transformation of (±)-**2** into (S)-**4** begins to emerge from these results (Scheme 3). The initial formation of a [Pd(*t*Bu-phox)(dba)] complex **5** precedes substrate coordination and oxidative addition to form carboxylate **1**, the resting state of the catalytic cycle. Turnover-limiting decarboxylation produces enolate **6**, which undergoes rapid C–C bond-forming reductive elimination (the enantiodetermining step) to form (S)-**4** and a

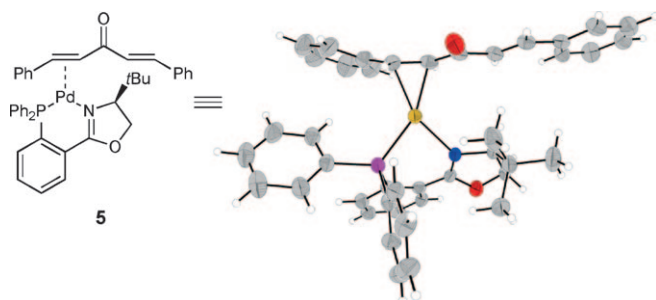
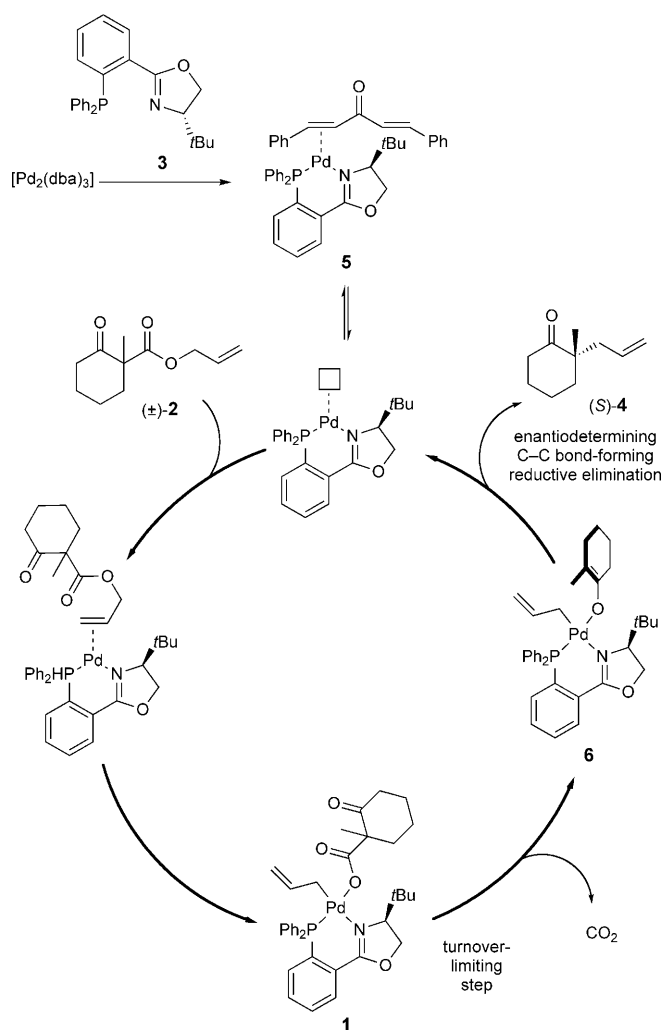


Figure 5. X-ray crystal structure of adduct **5**. The molecular structure is shown with 50% probability ellipsoids.^[6]



Scheme 3. Proposed mechanism.

palladium species capable of complexation with a further molecule of the substrate to continue the cycle. Alternatively, following the consumption of substrate (±)-**2**, complexation with dba produces complex **5** again.

In summary, we have detailed the mechanism of the early stages of our enantioselective allylic alkylation reaction on the basis of an experimental approach. We isolated and characterized all intermediates from the catalytic alkylation reaction of β-ketoester (±)-**2** that were observable by ³¹P NMR spectroscopy, including the *cis* η¹-σ-allyl intermediate **1**. We believe that the unique structure of **1** and the acetate counterpart **7** is of potential mechanistic significance to a broad range of reactions. Experimental mechanistic investigations into the decarboxylation, bond-forming, and stereoselective steps of our allylic alkylation reaction are currently underway.

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