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

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## Abstract

**Palladium poprocks: Hold on to your $CO_2$!** Enantioselective Pd-catalyzed decarboxylative alkylation of ketone enolates proceeds via $\eta^1$-σ-allyl Pd-carboxylate complexes by slow loss of $CO_2$.

### Keywords

allylic alkylation; asymmetric catalysis; palladium; carboxylate ligands; reaction mechanism

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

Initially, we sought to follow the catalytic reaction of a standard β-ketoester substrate, (±)-**2**, by $^{31}$P NMR. Combining (*S*)-*t*-BuPHOX (**3**) and $Pd_2(dba)_3$ in a 2.6: 1 ratio at room temperature for 30 min as specified in our standard alkylation procedure,[1] yielded a single new resonance at 18.8 ppm along with the signal for free ligand (**3**) at −5.95 ppm (Figure 2, A). The addition of β-ketoester (±)-**2** resulted in the complete disappearance of the resonance at 18.8 ppm and produced a long-lived resonance at 30.9 ppm (Figure 2, B). As the reaction forming ketone **4**

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neared completion, the long-lived intermediate slowly reverted to the original 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 due to air sensitivity and thermal instability well below 24 °C both in solution and as a solvent-free solid.[5] Interestingly, impure samples of **1** visibly expel a gas (presumably $CO_2$) in the solid state and effervesce in solvent.[6] After extensive experimentation, crystals of high purity and reasonable stability were isolated and crystallographically characterized as a mixture of diastereomers resulting from the use of racemic β-ketoester **2**. Complex **1** is a square planar 16-electron species with a σ-bound, $\eta^1$-allyl ligand trans to nitrogen and a β-ketocarboxylate ligand trans to phosphorous. By contrast, the analogous Pd(PHOX)allyl·$PF_6$ cationic complex displays $\eta^3$-π-allyl bonding in the solid state[3,6,7] as do related structures in solution.[8]

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

The structure of palladium complex **1** is noteworthy. The arrangement of the allyl and carboxylate ligands in intermediate **1** is similar to that of a structure previously calculated by DFT methods for a palladium allyl enolate complex (**6**).[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 (Figure 3). The high degree of structural similarity between intermediate **1** and complex **6** lends credence to this key calculated structure, and 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 CSD consisting of a palladium species with a β-ketocarboxylate ligand, but it is also the first X-ray structure of any transition metal complex with a σ-bound allyl 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 the immediately related decarboxylative allylic alkylation reactions,[1,10] but also for palladium catalyzed allylic oxidations,[11,12] palladium catalyzed 1,4-diacetoxylation,[11,13] and late transition metal-catalyzed decarboxylative reactions in general. With this in mind, we synthesized and crystallographically characterized the neutral $\eta^1$-allyl(PHOX)Pd(OAc) (**7**,Figure 4). Similar to carboxylate **1**, complex **7** is a 4-coordinate Pd(II) square planar species bearing a trans relationship of the phosphine and acetate. Despite its simplicity and central nature to many catalytic pathways, this canonical oxidative addition adduct of allyl acetate and $L_n$Pd(0) has not been previously characterized.[14] In light of the availability of $\eta^1$-allyl complexes **1** and **7**, it may be reasonable to consider analogous neutral intermediates in a variety of studies.[15]

With the catalyst resting state of the catalytic cycle identified, we studied the general reactivity of complex **1**. After 40 min in anhydrous THF at 24 °C, samples of intermediate **1** convert to the allylic alkylation product **4**, in 89% ee, which is consistent with the enantioselectivity observed in catalytic reactions conducted under our standard conditions (Scheme 2).[1] Allowing this thermal decomposition to occur in the presence of free dba ligand generates

complex **5** (Scheme 2).[16] Phosphorous-31 NMR indicated that this complex (**5**) was identical to the phosphorus-containing compound previously observed in the $^{31}$P NMR study described above (Figure 2, A and C). Additionally, complex **5** can be formed independently by mixing $Pd_2(dba)_3$ with (*S*)-*t*-BuPHOX (**3**), suggesting that complex **5** is the initial adduct in our, as well as other related, allylic alkylation systems,[10a,b,e] and is the predominant palladium-containing species in the absence of substrate.

We proceeded to isolate and characterize complex **5**, which was assigned by X-ray analysis to be monomeric Pd(PHOX)(dba) (Figure 5). Isolated **5** is a competent catalyst for the asymmetric alkylation reaction providing yields and enantiomeric induction analogous to that of our previously published procedures.[1,6]

A mechanistic picture for the transformation (±)-**2** → (*S*)-**4** begins to emerge with these results in hand (Scheme 3). Initial formation of a Pd(PHOX)(dba) (**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 and enantiodetermining reductive elimination to form (*S*)-**4** and a palladium species capable of engaging further substrate to continue the cycle. Alternatively, upon consumption of substrate (±)-**2**, complexation with dba produces complex **5** again.

In summary, we have experimentally detailed the mechanism of the early stages of our enantioselective allylic alkylation reaction. We have isolated and characterized all of the $^{31}$P NMR-observable intermediates from the catalytic alkylation reaction of β-ketoester (±)-**2**, including *cis*-$\eta^1$-σ-allyl intermediate **1**. We believe this unique structure (**1**) and the acetate counterpart (**7**) are 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## References


1. a) Mohr JT, Stoltz BM. Chem–Asian J 2007;2:1476–1491. [PubMed: 17935094] b) Mohr JT, Behenna DC, Harned AM, Stoltz BM. Angew Chem 2005;117:7084–7087.Angew Chem Int Ed 2005;44:6924–6927. c) Behenna DC, Stoltz BM. J Am Chem Soc 2004;126:15044–15045. [PubMed: 15547998] d) Seto M, Roizen JL, Stoltz BM. Angew Chem 2008;120:6979–6982.Angew Chem Int Ed 2008;47:6873–6876.
2. For instance, the addition of 0.55 equiv $H_2O$ to a typical reaction results in only marginal loss of yield and ee (<2% each). See supporting information for details.
3. Keith JA, Behenna DC, Mohr JT, Ma S, Marinescu SC, Oxgaard J, Stoltz BM, Goddard WA III. J Am Chem Soc 2007;129:11876–11877. [PubMed: 17824701]
4. To corroborate our investigation between all three variants of our allylic alkylation reaction, analogous $^{31}$P NMR experiments were performed for the equivalent conversion of allyl enol carbonate and silyl enol ether substrates to ketone **4** yielding similar results.[6]
5. At 24 °C, carboxylate **1** has a $t_{1/2}$ = 7.3 min in THF-$d_8$.
6. See supporting information for details.
7. The related (i-PrPHOX)Pd(diphenylallyl)Cl displays a similar 4-coordinate arrangement with an $\eta^1$-allyllic unit. For this complex and a discussion of other, rare $\eta^1$-allyl·Pd complexes, see: Kollmar M, Helmchen G. Organometallics 2002;21:4771–4775.
8. For comprehensive discussions, see: a) Kollmar M, Goldfuss B, Reggelin M, Rominger F, Helmchen G. Chem–Eur J 2001;7:4913–4927. b) Liu S, Müller JFK, Neuburger M, Schaffner S, Zehnder M. J Organomet Chem 1997;549:283–293.

9. Literature examples of transition metal complexes with a σ-bound allyl cis to a carboxylate ligand are limited to a single ruthenium and a single rhodium complex that are characterized by other methods See: a) Planas JG, Marumo T, Ichikawa Y, Hirano M, Komiya S. J Mol Catal A Chem 1999;147:137–154. b) Payne MJ, Cole-Hamilton DJ. J Chem Soc Dalton Trans 1997:3167–3175.
10. a) Bélanger É, Houzé C, Guimond N, Cantin K, Paquin JF. Chem Commun 2008:3251–3253. b) Bélanger É, Cantin K, Messe O, Tremblay M, Paquin JF. J Am Chem Soc 2007;129:1034–1035. [PubMed: 17263376] c) Waetzig SR, Rayabarapu DK, Weaver JD, Tunge JA. Angew Chem 2006;118:5099–5102.Angew Chem Int Ed 2006;45:4977–4980. d) Trost BM, Bream RN, Xu J. Angew Chem 2006;118:3181–3184.Angew Chem Int Ed 2006;45:3109–3112. e) Nakamura M, Hajra A, Endo K, Nakamura E. Angew Chem 2005;117:7414–7417.Angew Chem Int Ed 2005;44:7248–7251. f) Trost BM, Xu J. J Am Chem Soc 2005;127:2846–2847. [PubMed: 15740108]
11. a) Grennberg H, Langer V, Bäckvall JE. J Chem Soc Chem Commun 1991:1190–1192. b) Bäckvall JE, Hopkins RB, Grennberg H, Mader MM, Awasthi AK. J Am Chem Soc 1990;112:5160–5166.
12. a) Moiseev II, Vargaftik MN. Coord Chem Rev 2004;248:2381–2391. b) Hansson S, Heumann A, Rein T, Åkermark B. J Org Chem 1990;55:975–984. c) Byström SE, Larsson EM, Åkermark B. J Org Chem 1990;55:5674–5675. d) Åkermark B, Hansson S, Rein T, Vågberg J, Heumann A, Bäckvall JE. J Organomet Chem 1989;369:433–444.
13. Bäckvall JE, Byström SE, Nordberg RE. J Org Chem 1984;49:4619–4631.
14. For structures of $\eta^3$-allylic Pd, Pt, and Ni complexes with noncoordinating trifluoroacetate and bicarbonate counterions, see: a) Böttcher L, Scholz A, Walther D, Weisbach N, Görls H. Z Anorg Allg Chem 2003;629:2103–2112. b) Dervisi A, Edwards PG, Newman PD, Tooze RP, Coles SJ, Hursthouse MB. J Chem Soc Dalton Trans 1999:1113–1120. c) Jacob V, Weakley TJR, Haley MM. Organometallics 2002;21:5394–5400. d) Pawlas J, Nakao Y, Kawatsura M, Hartwig JF. J Am Chem Soc 2002;124:3669–3679. [PubMed: 11929257] e) Ozawa F, Son T-i, Ebina S, Osakada K, Yamamoto A. Organometallics 1992;11:171–176.
15. Neutral $\eta^2$-olefin complexes have been previously postulated to be long-lived states, prior to oxidative addition, in related allylic alkylations. It has also been assumed that the product of oxidative addition leads directly to a cationic $\eta^3$-allyl complex. For examples, see: a) Evans LA, Fey N, Harvey JN, Hose D, Lloyd-Jones GC, Murray P, Orpen AG, Osborne R, Owen-Smith GJJ, Purdie M. J Am Chem Soc 2008;130:14471–14473. [PubMed: 18839958] b) Amatore C, Gamez S, Jutand A. Chem–Eur J 2001;7:1273–1280.
16. The enantioselectivity of the reaction to produce ketone **4** is insensitive to the presence of 3.0 equiv dba in solution.

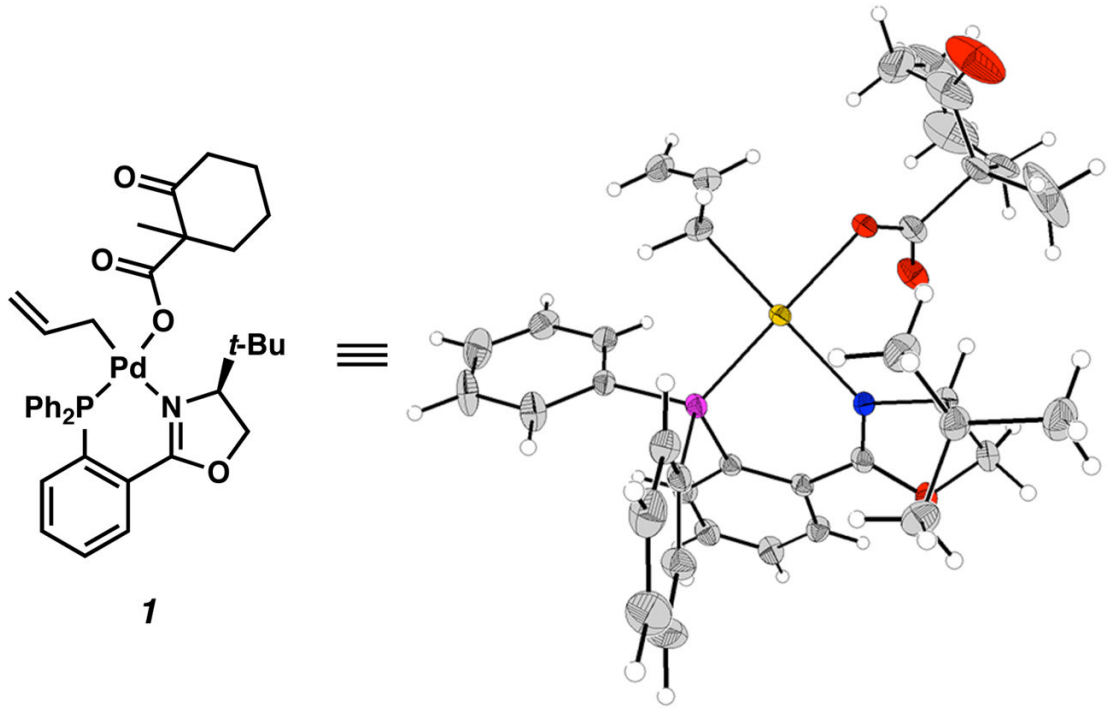



**Figure 1.**
X-ray structure of complex **1** (one diastereomer shown), the resting state of the catalytic cycle. The molecular structure is shown with 50% probability ellipsoids.

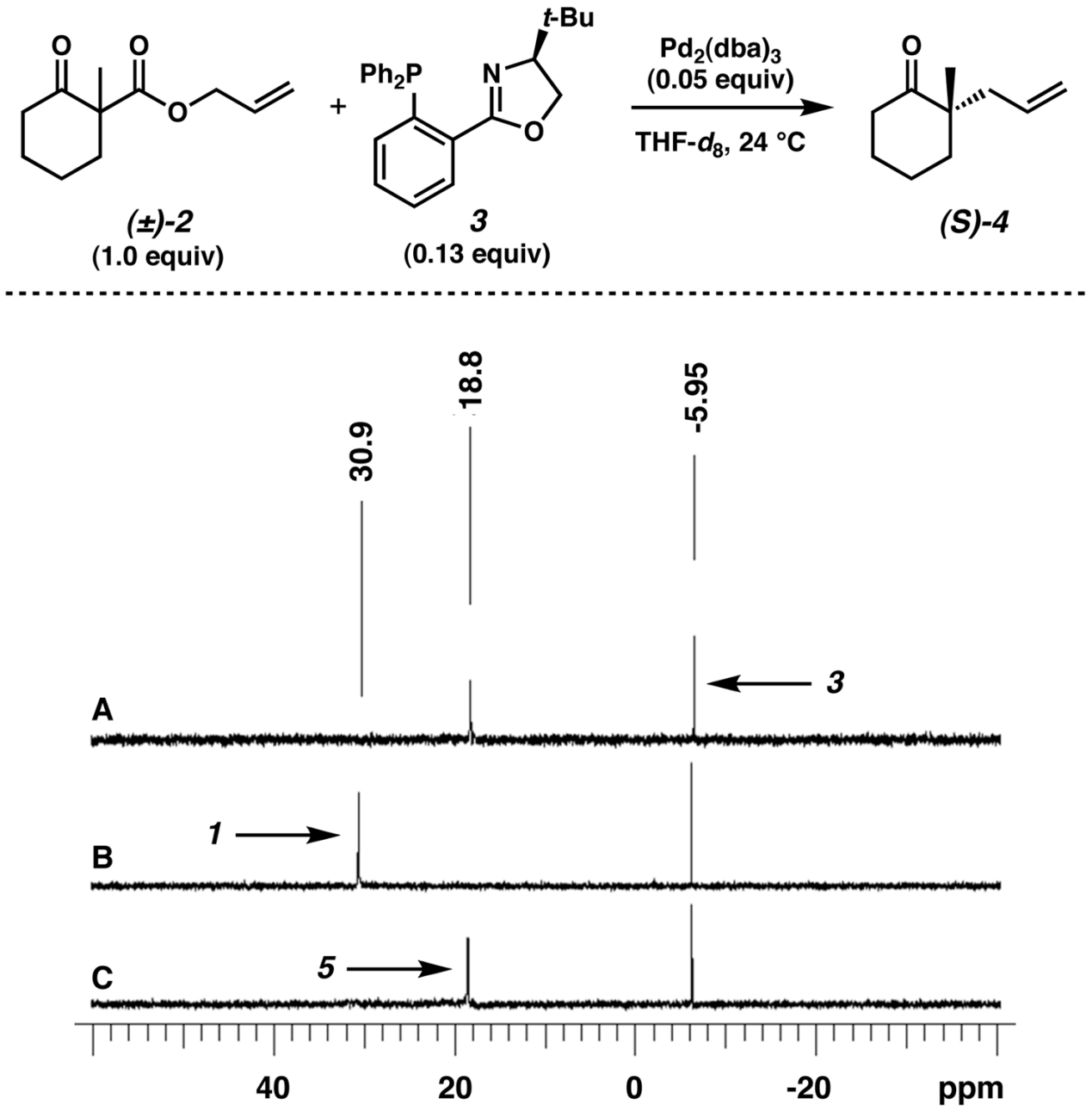



**Figure 2.**

$^{31}$P NMR study of the asymmetric allylic alkylation of β-ketoester (±)-**2**. A) Spectrum of ligand **3** and $Pd_2(dba)_3$ in THF-$d_8$ after 30 min. B) Spectrum after addition of β-ketoester (±)-**2** to the above mixture. C) Spectrum after completion of the reaction to form ketone **4**. Spectra referenced to 85% aq $H_3PO_4$, δ 0.0 ppm.

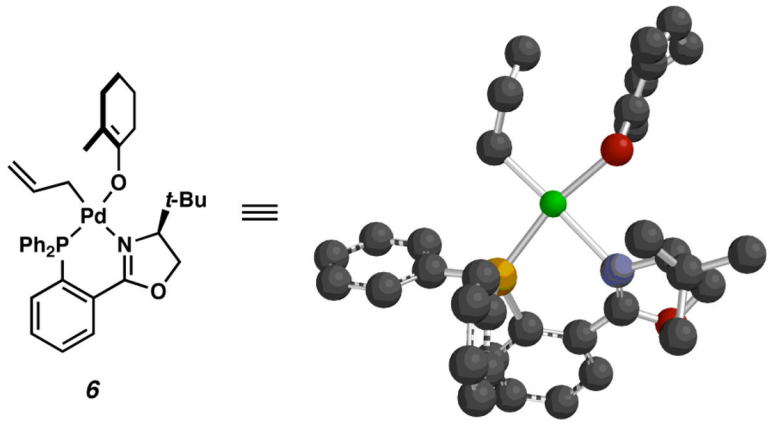



**Figure 3.**
DFT-calculated intermediate $\eta^1$-allyl Pd-enolate, prior to C–C bond-forming reductive elimination.[3] Hydrogen atoms have been removed for clarity.

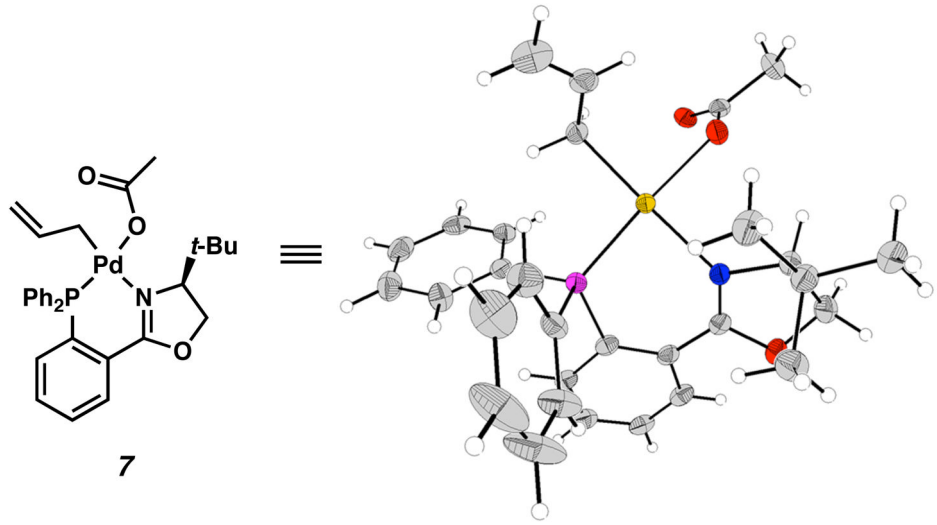



**Figure 4.**
X-ray structure of acetate **7** (one conformation represented). The molecular structure is shown with 50% probability ellipsoids.

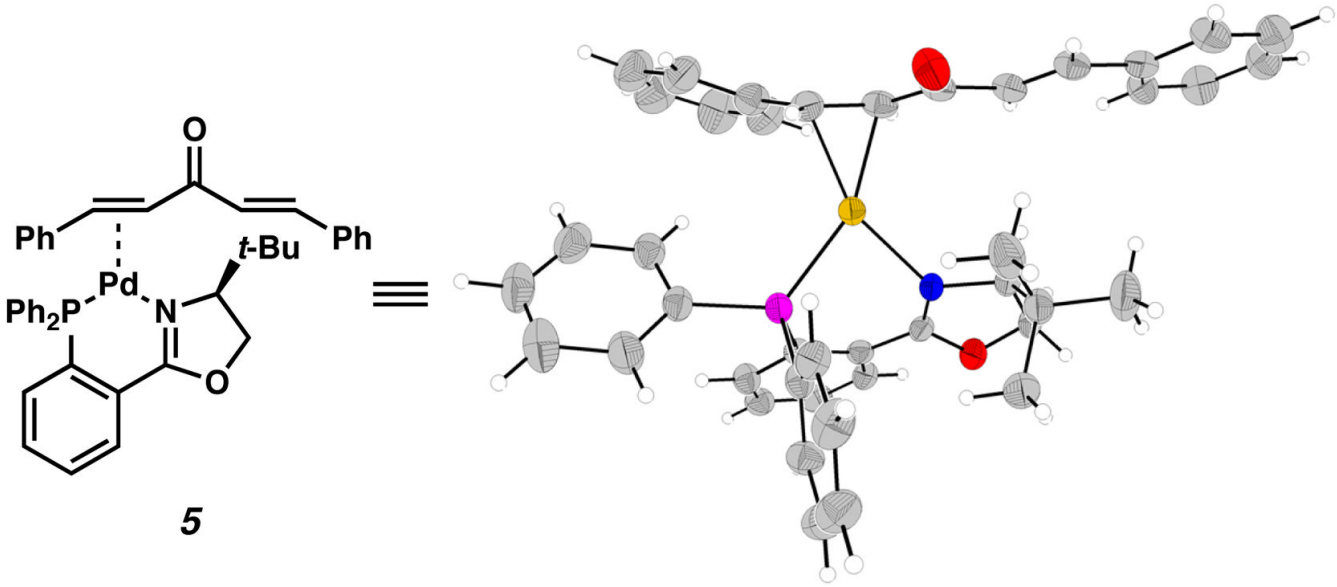
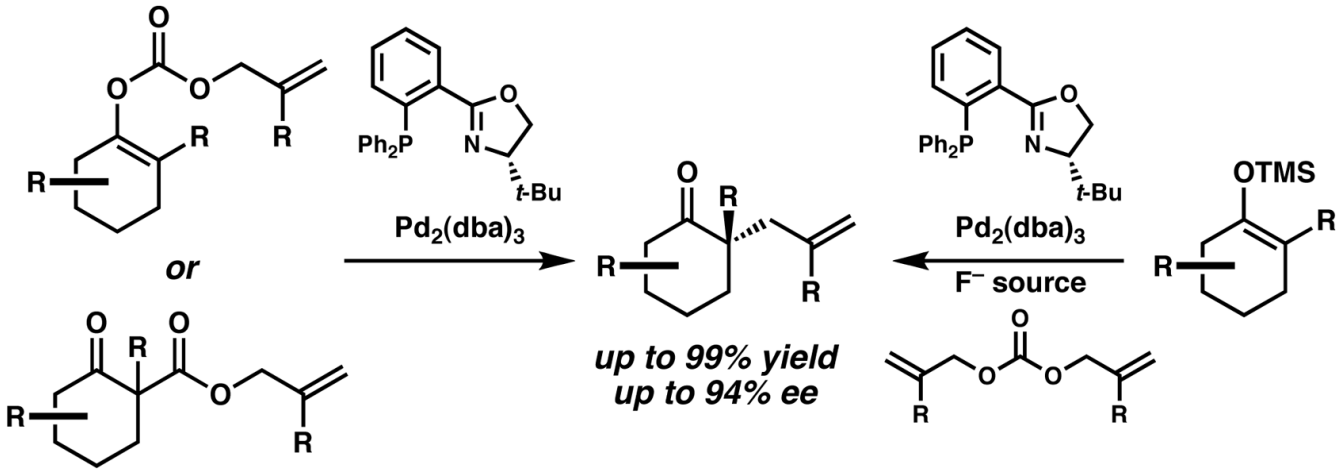
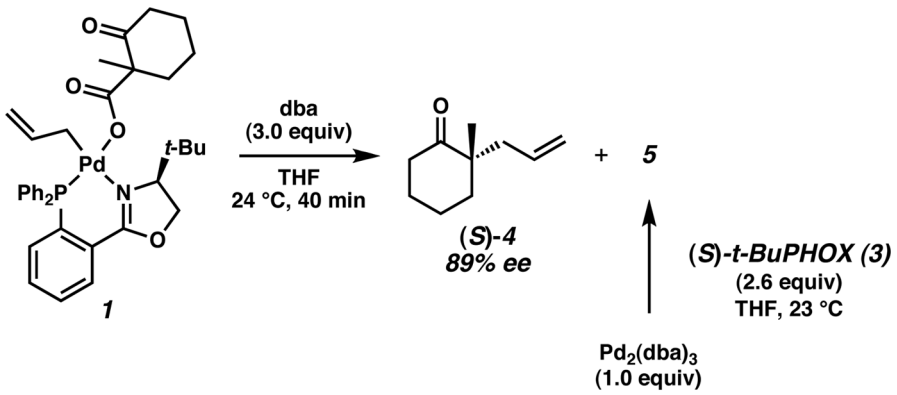



**Figure 5.**
X-ray structure of adduct **5**. The molecular structure is shown with 50% probability ellipsoids. [6]

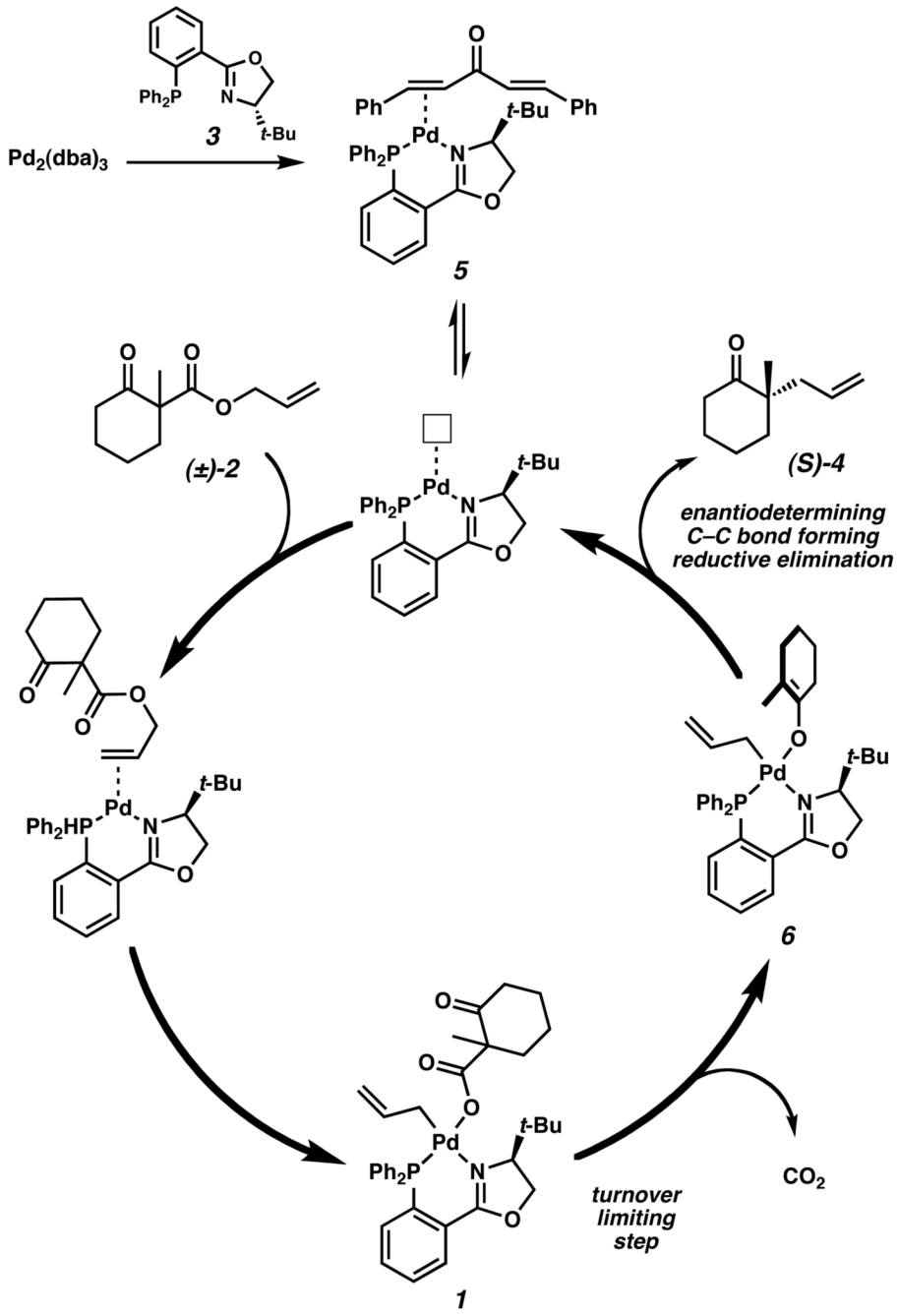



**Scheme 1.**
Palladium-catalyzed enantioselective decarboxylative allylic alkylations of ketone enolates. dba = *trans*,*trans*-dibenzylideneacetone.




**Scheme 2.**

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




**Scheme 3.**
Proposed mechanism.