Palladium Complexes

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Palladium-Catalyzed Allylic Substitution at Four-Membered-Ring Systems: Formation of η^1-Allyl Complexes and Electrocyclic Ring Opening**

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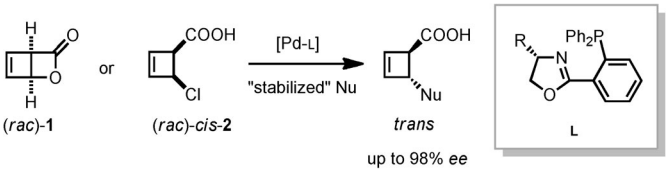
Palladium allyl complexes have been extensively studied over the past decades owing to their relevance in homogeneous catalysis. They represent key intermediates in catalytic allylic substitution reactions (Tsuji–Trost reactions) and considerable efforts have been made to elucidate their solution structures and mechanistic behavior in detail.[1] 1,3-Diphenylpropenyl acetates and carbonates are the benchmark linear systems employed for the study of allyl palladium intermediates.[2] When cyclic substrates are concerned, cycloalk-2-enyl esters are often biased by undesired β-hydride elimination events, which critically affect the stability of the resulting metal complexes as they rapidly lead to the corresponding cycloalkyldiene byproducts.[3,4] To date, palladium allyl complexes derived from five- and four-membered-ring systems have been virtually unexplored.[4]

We recently reported a diastereodivergent synthesis of 3,4-disubstituted cyclobutenes through a deracemizing palladium-catalyzed asymmetric allylic alkylation.[5] In those studies, we uncovered unprecedented behavior of the allylic electrophiles (*rac*)-**1** and (*rac*)-*cis*-**2** in the presence of phosphino-oxazoline ligands L (Scheme 1): nucleophilic attack by stabilized carbanions (i.e. malonates, azlactones, β-ketoesters) at the putative η^3-allyl intermediate took place to afford the *trans*-cyclobutene products in excellent levels of diastereo- and enantioselectivity.

This unusual reactivity of four-membered cyclic systems in the presence of ligands L along with the lack of literature precedent in the field warranted further investigation. Herein we present our preliminary findings on the unique structure and reactivity of cyclobuten-3-yl palladium complexes as well as the unprecedented electrocyclic ring opening of an organopalladium derivative.



Scheme 1. Stereoselective synthesis of *trans*-disubstituted cyclobutenes from (*rac*)-1 and (*rac*)-*cis*-2 with overall inversion of configuration. Nu = nucleophile.

The addition of stoichiometric amounts of L-Ph and $[Pd(dba)_2]$ (dba = *trans*,*trans*-dibenzylideneacetone) to the substrate (*rac*)-*cis*-**2** proceeded instantaneously at −30 °C (Scheme 2). The thus formed intermediate **3** is unstable at room temperature. Nevertheless, it could be extensively characterized by multinuclear NMR spectroscopy at 10 °C as a η^1-allyl complex (Scheme 2). The ^{13}C NMR spectrum was diagnostic for a η^1-allyl ligand, with characteristic chemical shifts at 129.1, 147.9, and 46.0 ppm for C2, C3 and C4 (bearing Pd), respectively.[6] Consistent with literature precedence for the arrangement of ligands around square-planar Pd^{II} centers, the η^1-allyl moiety is located *trans* to the nitrogen donor of L-Ph, a ligand of weaker *trans* influence than phosphorus.[7] This configuration was determined by NMR analysis: the small coupling constant $^2J_{CP} = 4.3$ Hz indicates a *cis* relationship across the Pd center,[8] while the experimental NOE data for the ^1H atoms at positions 1 and 4 indicates an *anti* configuration of the substituents on the cyclobutene.

Although η^3/η^1 slippage of allyl ligands plays a major role in the Tsuji–Trost reaction and constitutes one of the critical issues in the control of regio- and stereoselectivity, only a few examples of isolated η^1-allyl species have been reported.[9] In addition, the combination of a chiral racemic substrate such as **2** with an enantiopure Pd–L complex could be expected to yield two diastereomeric species. Remarkably, one of these two possible diastereoisomeric complexes is largely dominant (d.r. > 7:1). This strongly suggests that deracemization of *cis*-**2** takes place during the very rapid oxidative addition step at −30 °C.

When sodium diethyl (2-methyl)malonate was added to the preformed complex **3** at 0 °C, the *trans*-cyclobutene product **5** was obtained with 96 % *ee* (Scheme 2). This result

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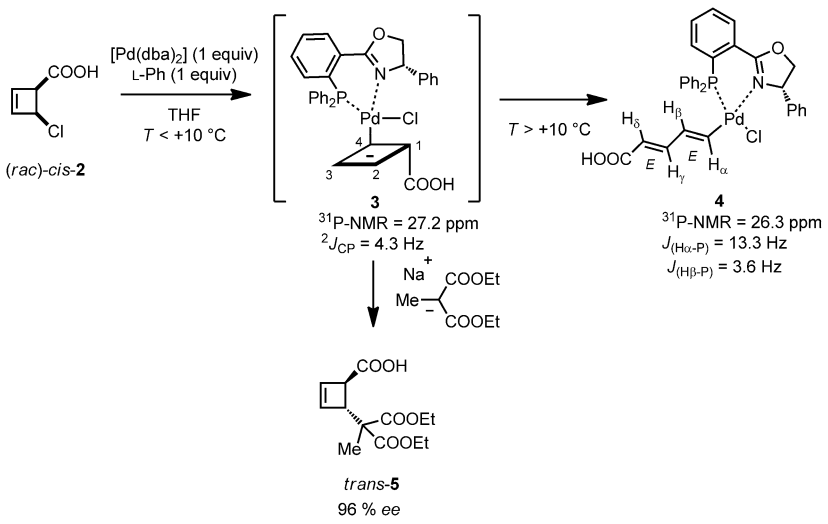


Scheme 2. Formation of η^1-allyl complexes and subsequent electrocyclic ring opening.

is consistent with the observed enantioselectivity in the catalytic reactions that we reported previously,[5b] demonstrating that **3** is a catalytically active reaction intermediate.[10]

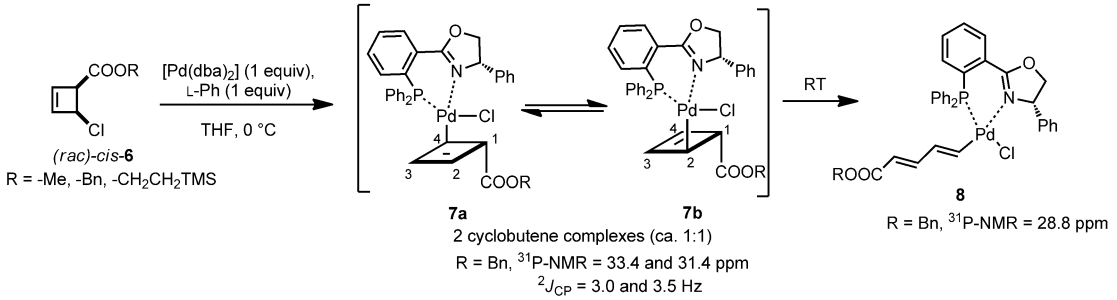
When a sample of **3** is held at room temperature, the ^{31}P NMR resonance at $\delta = 27.2$ ppm slowly disappears while a new signal at $\delta = 26.3$ ppm is observed. This new metastable species was identified as the palladium (*E*,*E*)-diene complex **4**,[11] the product of the formal thermal conrotatory 4π-electrocyclic ring opening of *trans*-**3**.[12] Especially informative is the coupling observed between the protons H_α and H_β of the diene and the phosphorus of L-Ph ($J_{H\alpha\text{-}P} = 13.3$ Hz, $J_{H\beta\text{-}P} = 3.6$ Hz).

Diene complex **4** was also obtained by reacting the preformed diene (*E*,*E*)-5-chloropenta-2,4-dienoic acid with L–Ph and a palladium(0) precursor, through a more conventional oxidative addition at the C–Cl bond.[13] To the best of our knowledge, this is the first report of an electrocyclic ring opening of an organopalladium derivative.[14] Remarkably, while oxidative additions of aromatic halides to palladium(0) centers have been extensively studied, palladium(II) vinyl complexes are much less common and scarcely reported in the literature.[15]

We subsequently explored the reactivity of the esters (*rac*)-*cis*-**6** (Scheme 3). In our previous work,[5b] these compounds had proved surprisingly unresponsive under catalytic conditions in the presence of ligands L. In sharp contrast to (*rac*)-*cis*-**2**, the stoichiometric combination of several derivatives of **6** and Pd–L complexes led to the formation of a 1:1 mixture of isomers (for R = Bn, ^{31}P NMR resonances at $\delta = 33.4$ and 31.4 ppm, respectively). Thus, in the presence of an ester moiety, the ligand L-Ph is not able to promote rapid deracemization through the oxidative addition step as before. 2D-NMR analysis at low temperature (+5 °C) confirmed both **7a** and **7b** to be η^1-allyl complexes, existing in a dynamic equilibrium in solution; EXSY/NOESY experiments highlighted a slow interconversion, based on clear exchange cross-peaks between ^{1}H at positions 1, 2, 3, and 4 of **7a** with positions 1, 4, 3, and 2 of **7b**, respectively. Furthermore, no η^3-allyl species were detected in the reaction mixture at any time. At room temperature, both species are converted into the same (*E*,*E*)-diene complex **8** (^{31}P NMR $\delta = 28.8$ ppm), strongly suggesting **7a** and **7b** to be a diastereomeric pair. Although the oxidative addition proceeds smoothly, intermediates **7a**,**b** do not undergo nucleophilic addition by malonate salts at room temperature or below. This is in agreement with their recalcitrance under catalytic conditions.[16]

These unprecedented observations warranted further mechanistic investigation. We thus performed DFT calculations at the BP86/def2-SVP level to elucidate the underlying reaction mechanisms (see the Supporting Information for the chosen methods, detailed numerical results, and the structures of all stationary points). After considering 49 possible starting configurations, we were able to identify two energetically low-lying η^1-allyl complexes (**7a** and its diastereomer **7b**; R = CH_3). Pathways for the electrocyclic ring-opening reactions and relevant transition states were located for complexes **7a** and **7b**, with free energy barriers of 17.3 and 19.0 kcal mol^{-1}, respectively (Figure 1). The relatively slow ring-opening reaction, resulting in the (*E*,*E*)-diene complex **8**, is consistent with these fairly large computed barriers.

In the lowest-energy transition state for the electrocyclic ring opening of **7a** (TS_{ring}-**1**; Figure 2), the breaking C–C bond is lengthened from 1.58 Å in **7a** to a value of 2.17 Å, which is typical for this type of reaction, while the Pd–C bond is shortened from 2.07 Å to 1.99 Å, with almost no change in the other Pd–X bond lengths (X = N, P, Cl). The Pd-C1-C2-C3 dihedral angle amounts to 135.2°, while the corresponding value for C5-C4-C3-C2 is 142.7°, clearly indicating a conrota-



Scheme 3. Formation of four-membered-ring η^1-allyl complexes from ester *cis*-**6**. Bn = benzyl, TMS = trimethylsilyl.

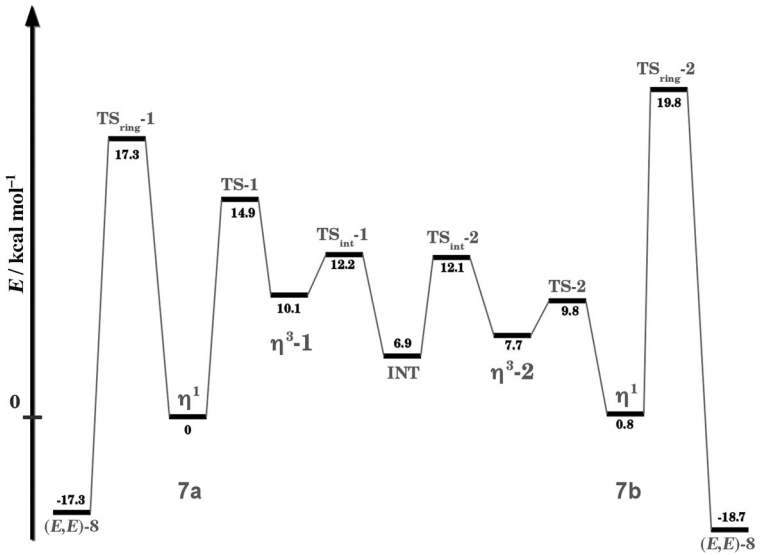


Figure 1. Computed free energy profile (25 °C) for the ring opening and η^1-η^3-η^1 interconversion pathway at the BP86/def2-SVP level. See Figures S1–S13 in the Supporting Information for the structures of all stationary points. INT = intermediate, TS = transition state, TS_{Int} = transition state for the rearrangement to the intermediate, TS_{Ring} = transition state for the ring opening.

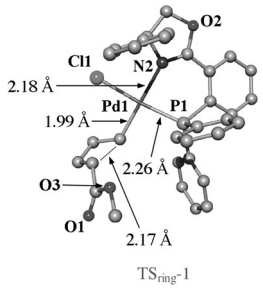


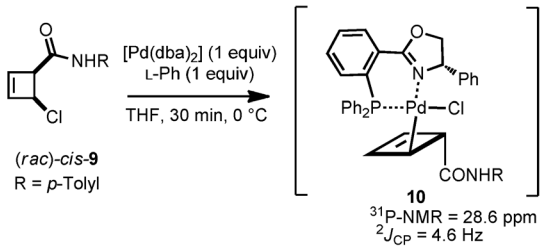
Figure 2. Optimized geometry of TS_{ring}-**1** at the BP86/def2-SVP level. The hydrogen atoms are omitted for clarity (see Figure S1 in the Supporting Information for more details).

tory ring-opening mode (see Figure S15 for the HOMO of TS_{ring}-**1**).

We also identified a η^1-η^3-η^1 interconversion mechanism which proceeds through a common intermediate, INT (Figure 1), where the Pd–N bond to the imino fragment of the ligand is formally broken. The highest-energy transition state for the multistep interconversion pathway is computed to lie 14.9 kcal mol^{-1} above **7a** and is thus placed energetically below the ring-opening transition states (Figure 1).[7] The largest individual free energy barriers for the interconversion between **7a** and **7b** are 14.9 (9.0) kcal mol^{-1} in the forward (backward) direction. These results suggest a scenario of isomer interconversion through allyl slippage which occurs more readily than the irreversible ring-opening to the diene.

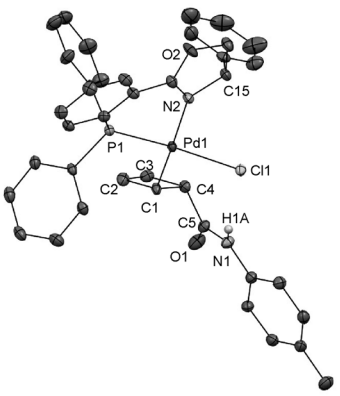
Finally, the reactivity of the secondary amide *cis*-**9** was explored. In analogy with the acid *cis*-**2**, the formation of essentially a single η^1-allyl species **10** was observed in the presence of stoichiometric amounts of the Pd–(L-Ph) complex (>14:1 ratio) (Scheme 4). Unambiguous proof of the structure and *anti* configuration of the η^1-allyl palladium complex **10** was achieved by single-crystal X-ray crystallographic analysis (Scheme 4).[17] Although transition-metal complexes of cyclobutene have been reported,[14e,g,18] analogous palladium complexes bearing β-hydrogens are hitherto unknown.[3,4] It appears that the antiaromatic nature of the cyclobutadiene product that would be generated through β-hydrogen elimination is a key element ensuring the stability of this palladium complex, thus allowing us to determine its crystal structure. Interestingly, the distance between the chloride and the N-H hydrogen is 2.427 Å, which implies there is a hydrogen bond between the two atoms (cf. sum of van der Waals radii for H and Cl: 1.2 + 1.75 = 2.95 Å).[19] It is possible that a similar hydrogen bond may be present in complex **3**, and this may be an important factor in achieving deracemization upon formation of Pd–L complexes.

The sum of the angles surrounding the palladium center amounts to 361.4°, indicating that complex **10** has a slightly distorted square-planar coordination geometry. This is in contrast with the previously reported structures of η^1-allyl Pd complexes with bidentate P,N ligands[9] where this sum has been found to lie in a narrow range between 359.9 and 360.1. The length of the C1–C4 bond is 1.599 Å, while in a typical cyclobutene (e.g., *cis*-**2**) the corresponding bond length is 1.574 Å.[20] This C–C bond elongation is likely a consequence of the η^1-coordination to palladium. In



distances /Å	
C1-C2	1.513(5)
C1-C4	1.599(5)
C2-C3	1.335(5)
C3-C4	1.511(5)
C1-Pd1	2.055(3)
N2-Pd1	2.120(2)
P1-Pd1	2.2108(9)
Cl1-Pd1	2.4200(8)
Cl1-H1A	2.427

angles /deg	
C2-C1-C4	84.7(2)
C3-C2-C1	95.2(3)
C2-C3-C4	94.7(3)
C3-C4-C1	85.2(2)
C1-Pd1-P1	93.68(12)
N2-Pd1-P1	86.28(10)
C1-Pd1-Cl1	91.04(11)
N2-Pd1-Cl1	90.43(10)
C1-Pd1-N2	172.81(14)
P1-Pd1-Cl1	167.88(3)



Scheme 4. Preparation and single-crystal X-ray structure of the four-membered-ring η^1-allyl complex **10**.

addition, the angle C2-C1-C4 is distorted from 86.3° to 84.7°. Although these deviations are small, this ensemble of structural data is entirely consistent with an increased propensity of the η^1-allyl-cyclobutene complexes prepared in this work towards electrocyclic ring opening. It is remarkable to note how the two remote chiral centers of ligand L-Ph are capable of orchestrating the deracemization of the η^1-allyl fragment at a distance of three bonds (C15-N2-Pd-C1/C4).

In conclusion, we have shown compelling evidence for a remarkably fast deracemization during the addition of Pd–L species to suitable electrophiles. In particular, rare examples of η^1-allyl palladium complexes of cyclic systems, especially bearing β-hydrogens are reported herein, including unique crystallographic evidence. Their unprecedent propensity for electrocyclic ring opening is described, and the relevance of these findings is also discussed from a structural and computational perspective. Further work aimed at probing the reactivity of the η^1-allyl palladium complexes described in this article, as well as preparative studies employing other ligand types, is underway and will be disclosed in due course.

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[10] The mechanism accounting for the formation of *trans*-**5** upon reaction of **3** with the malonate nucleophile is intriguing. One might consider coordination of the anion followed by reductive elimination, a pathway that has, to the best of our knowledge, never been observed for allylic alkylations with stabilized ("soft") nucleophiles. Alternatively, inversion at the metal-bonded carbon should precede nucleophilic attack. Attempts to assess this situation have been unproductive thus far.

[11] The coupling constants of protons H_α ($^3J_{HH} = 14.8$ Hz) and H_δ ($^3J_{HH} = 15.2$ Hz) were in agreement with this assignment.

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[16] When malonate nucleophiles were added to preformed intermediates **7a** and **7b** only decomposition was observed after 15 h at 0 °C. See Ref. [5b].

[17] CCDC 931148 (**10**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for more details.

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[20] See the Supporting Information for a comparative tabular listing of C–C bond lengths in several cyclobutene carboxylic acids.

