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Evidence for a Non-Concerted, Dissoziative Mechanism of the Palladium-Catalyzed "Enolate Claisen Rearrangement" of Allylic Esters

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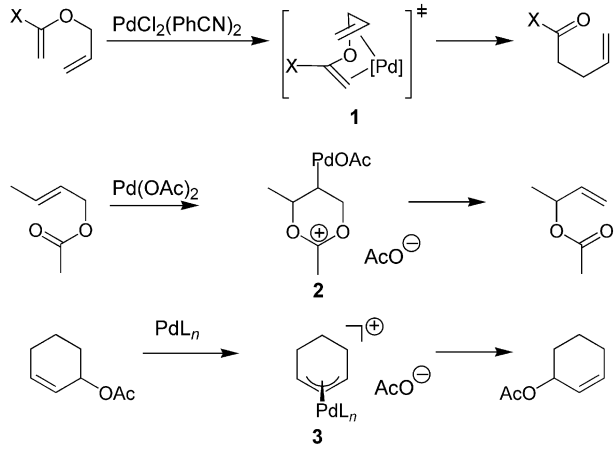
In an enolate Claisen rearrangement, deprotonated allyl phenylacetate undergoes a smooth conversion at –78 °C to 2-phenyl-4-pentenoic acid under palladium(0) catalysis. By using labelled starting materials in crossover experiments, the reaction is shown to follow a dissoziative, non-concerted, non-[3,3]-sigmatropic mechanism that involves palladium complexes and carboxylic-acid dianions as intermediates.

Introduction

The Claisen rearrangement, diversified in various variants, is one of the most versatile and powerful reactions that permit carbon-carbon bond formations.[1] The questions of the mechanism and the exact nature of the transition state with its stereochemical implications have been studied thoroughly, and it is generally accepted that the Claisen rearrangement of allyl vinyl ethers as well as the Ireland–Claisen and the enolate Claisen rearrangement follow a concerted, albeit asynchronous, [3,3]-sigmatropic path.[2] It is not surprising that intense efforts have been directed towards a metal catalysis for these reactions.[3] This approach has become particularly efficient when chiral metal complexes were used to bring about enantioselective Claisen-type rearrangements starting form prochiral precursors.[4] Aside from main group metal based Lewis-acidic salts and complexes, copper and, in particular, palladium catalysts enjoyed manifold applications.[5] The activation by the late transition metals has been attributed to a coordination of the carbon-carbon π-bonds in the transition state model **1**,[4,5c] illustrated for palladium(II) in Scheme 1. However, the concerted course of palladium(II)-mediated Claisen rearrangements is challenged by the cyclization-induced rearrangement mechanism[5a] (Scheme 1) that was first proposed by Winstein[6] and supported by Henry[7] when explaining the palladium(II)-induced rearrangement of allylic acetates. This mechanism postulates a σ-palladium intermediate **2**,[3a,5a] an idea that has not only been adopted to the palladium(II)-mediated rearrangement of allyl vinyl ethers[3a,5a] and allyl imidates,[8] but also to the Ireland–Claisen rearrangement of silyl ketene acetals.[9] Despite the postulated intermediate **2**, the [3,3]-sigmatropic, intramolecular course is maintained. When, however, allylic acetates are rearranged in the presence of palladium(0) catalysts, a dissociation occurs with formation of a cationic allylpalladium complex **3**.[10] taking advantage of the readily replaced leaving group acetate. This mechanism has been assumed for various palladium(0)-mediated Claisen-type rearrangements of allyl phosphoro and phosphonothionates[11a] and allyllic esters of *N*-alkylidene glycine[11b] as well as the allylic allylation through allyl enol carbonates,[12] originally reported by Tsuji.[12a]



Scheme 1. Mechanisms of palladium-catalyzed Claisen rearrangements.

The so-called simple-enolate Claisen rearrangement (Scheme 2) differs from the Ireland–Claisen rearrangement and is defined as the reaction of enolates derived from allylic esters, wherein the enolate-counterion is an alkali or an earth alkali metal.[13a] A concerted course has been postulated for this reaction as well as for the related chelate-enolate Claisen rearrangement.[13b] When, however, the latter reaction was mediated by palladium, an intermolecular

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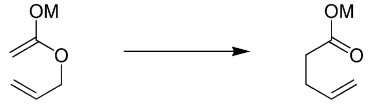
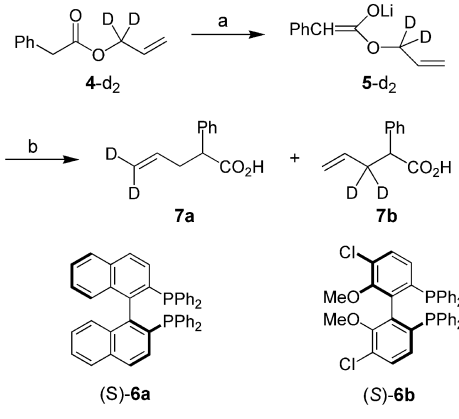
course was shown to occur.[14] To the best of our knowledge, the influence of palladium(0) complexes on the Claisen rearrangement of simple, non-stabilized enolates has not been reported. Therefore, we have studied the rearrangement of lithium enolates generated by deprotonation allyl phenylacetate in the presence of palladium(0) catalysts.



Scheme 2. The simple-enolate Claisen rearrangement of allylic esters: M = Li, Na, MgX.

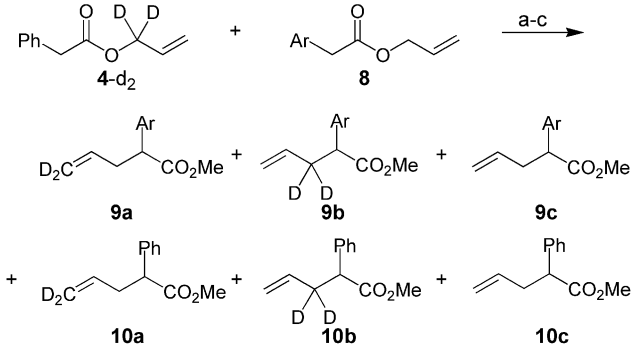
Results and Discussion

The [3,3]-sigmatropic character of the rearrangement was studied first. For this purpose, dideuterated allyl phenylacetate **4**-d_2 (Scheme 3) was deprotonated with lithium diisopropylamide in THF in the presence of lithium chloride to give the lithium enolate **5**-d_2. When left at room temperature overnight, no reaction took place and unchanged ester **4**-d_2 was re-isolated in quantitative yield.[15] However, when the lithium enolate was treated with $[Pd_2(dba)_3]\cdot CHCl_3$ (0.5 mol-%) and (*S*)-BINAP (**6a**) (2 mol-%), again in the presence of lithium chloride, the formation of 2-phenyl-4-pentenoic acid occurred at –78 °C. NMR analysis revealed a scrambling of the deuterium labels: Thus, 3,3-dideuterated and 5,5-dideuterated acids **7a** and **7b**, respectively, resulted as a 1:1 mixture in 73% combined yield. In addition, minor amounts of phenylacetic acid and tetradeuterated allyl 2-phenyl-4-pentenoate were detected by GC analysis. For reasons of comparison, the Ireland–Claisen variant was applied to the lithium enolate **5**-d_2 as well. Addition of chlorotrimethylsilane and warming to room temperature led, as expected, to 5,5-dideuterated acid **7a** exclusively after acidic work up. Thus it was concluded that, in contrast to the Ireland–Claisen version, the palladium-mediated simple-enolate rearrangement is not a [3,3]-sigmatropic shift.



Scheme 3. Palladium-catalyzed enolate Claisen rearrangement of deuterated allyl phenylacetate **4**-d_2. Reagents and conditions: a) LiN(*i*Pr)$_2$, THF, –78 °C; b) $[Pd_2(dba)_3]\cdot CHCl_3$ (0.5 mol-%), **6a** (2 mol-%), LiCl (2.4 equiv.), THF, –78 °C; then: NH_4Cl, H_2O.

Then, the question of an intramolecular vs. intermolecular mechanism was investigated by a crossover experiment that started from equal molar amounts of dideuterated ester **4**-d_2 of phenylacetic acid and non-deuterated allyl (4-chlorophenyl)acetate **8**. The mixture was deprotonated to give the corresponding lithium enolates and treated with $[Pd_2(dba)_3]\cdot CHCl_3$ (0.5 mol-%), *(S)*-**6a** (2 mol-%) and lithium chloride (2.4 equiv.) following the protocol described above. Prior to the mass spectrometric analysis, whose result is shown in Scheme 4, the crude mixture of carboxylic acids was transferred into the methyl esters **9** and **10** by treatment with trimethylsilyl diazomethane. GC–MS analysis of the crude methyl esters revealed the formation of a mixture of **9a**–**c** and **10a**–**c**. In the rearranged products **9a**–**c** with the 4-chlorophenyl substituent, the distribution of deuterated **9a/9b** to non-deuterated **9c** was found to be $50 \pm 4 : 50 \pm 4$. Correspondingly, the deuterated and non-deuterated esters **10a/10b** and **10c**, respectively, were obtained in essentially the same ratio of $45 \pm 4 : 55 \pm 4$ The scrambling of the labels, deuterium and the *para*-chloro substituent, in the products clearly excludes an intramolecular mechanism for the palladium(0)-catalyzed simple-enolate Claisen-rearrangement.



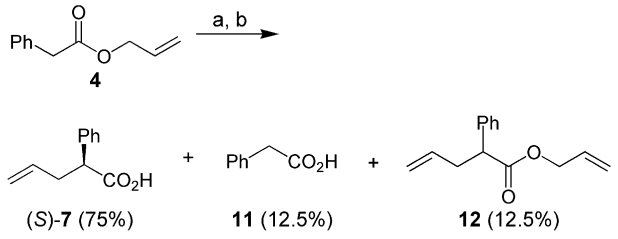
8, **9**: Ar = 4-ClC_6H_4

	4-d_2 : **8**	**9a/9b** : **9c**	**10a/10b** : **10c**
relative distribution	50 : 50	50±4 : 50±4	45±4 : 55±4

Scheme 4. Crossover experiment of the palladium-catalyzed rearrangement of lithium enolates of allylesters **4**-d_2 and **8**. Reagents and conditions: a) LiN(*i*Pr)$_2$, THF, –78 °C; b) $[Pd_2(dba)_3]\cdot CHCl_3$ (0.5 mol-%), (*S*)-**6a** (2 mol-%), LiCl (2.4 equiv.), THF, –78 °C; then: NH_4Cl, H_2O; c) Me_3SiCHN_2.

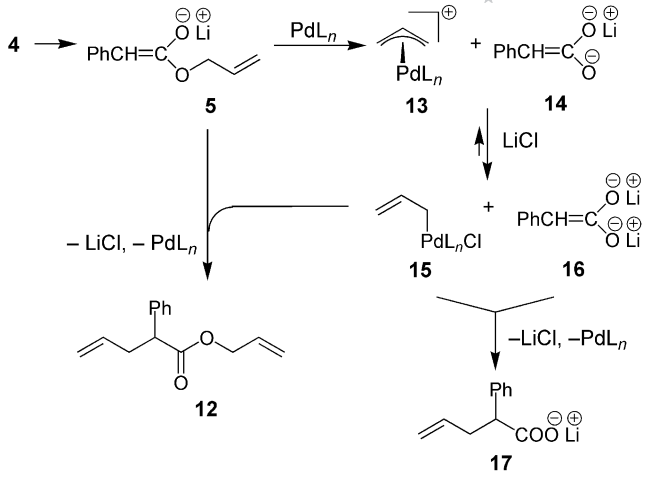
The stereochemical outcome of the palladium-mediated enolate Claisen rearrangement was studied with allyl phenylacetate (**4**) through the lithium enolate **5** and mediated with (*S*)-Cl-MeO-BIPHEP (**6b**) as chiral ligand. As shown in Scheme 5, (*S*)-2-penyl-4-pentenoic acid (**7**) was obtained in 25% *ee*, determined by comparison of the optical rotation with that described in the literature[16] and chiral GC of the methyl ester, generated from acid **7** by treatment with trimethylsilyl diazomethane. In addition to the rearranged

product **7** obtained in 75% yield, phenylacetic acid **11** and ester **12** were formed in 12.5% yield each, according to GC–MS analysis.



Scheme 5. Enantioselective formation of carboxylic acid **7** by palladium-catalyzed enolate Claisen rearrangement. Formation of by-products **11** and **12**. Reagents and conditions: a) $LiN(iPr)_2$, THF, –78 °C; b) $[Pd_2(dba)_3]\cdot CHCl_3$ (0.5 mol-%), (*S*)-**6b** (2 mol-%), LiCl (2.4 equiv.), THF, –78 °C; then: NH_4Cl, H_2O.

A mechanism that is suitable to explain the results described above is proposed in Scheme 6. It is assumed that the ester enolate **5**, upon exposure to palladium(0), dissociates into an allylpalladium complex **13** and the "dianion" **14**. It has been shown that in the presence of lithium chloride, cationic η^3-palladium complexes **13** are converted into neutral η^1 complexes **15**.[17] Based thereupon, we postulate an equilibrium between the palladium complexes **13** and **15** to lie on the side of the latter. Concomitantly with the formation of the neutral complex **15**, the dilitiated carboxylic acid **16** is generated. The species of carboxylic-acid dianions is well know to result from double deprotonation of carboxylic acids.[18] Palladium complex **15** and dilithiated phenylacetic acid **16** will combine under carbon-carbon-bond formation to give the lithium carboxylate **17** that yields 2-phenyl-4-pentenoic acid (**7**) as the major product upon aqueous acidic workup. In the η^3-η^1-equilibrium of **13** and **15**, neither terminus of the allyl moiety is preferred, so that the observed scrambling of the deuterium labels between **7a** and **7b** becomes evident. The result of the crossover experiment (Scheme 4) is explained by a dissociation of the ion pair **13** and **14** or neutral complex **15** and dilithiated species **16**, where the individual partners escape from the solvent cage. The postulated palladium complex **15** can – to a minor extent – combine with the ester enolate **5** – an assumption that explains not only the formation of the ester **12** containing two allyl moieties, but also the formation of phenylacetic acid: as a part the palladium complexes switched to ester enolate **5**, the forsaken original partner, the dianion **14**, is finally hydrolyzed to phenylacetic acid. The presence of lithium chloride may also enhance the reactivity of the doubly deprotonated carboxylic acid due to the known influence on the aggregation of lithium halides on lithium enolates.[19] Indeed, the palladium-mediated rearrangement of the lithium enolate **5** does not occur in the absence of lithium chloride at –78 °C but requires enhancement of the temperature to 0 °C conditions that lead to an almost complete loss of enantioselectivity. These results are in accordance with the crucial role, lithium chloride was found to play in the enantioselective palladium-catalyzed allylic alkylation of ketone enolates.[20,21]



Scheme 6. Proposed mechanism of the palladium-catalyzed lithium enolate Claisen rearrangement of allyl phenylacetate (**4**).

Conclusions

In summary, we have shown for the first time that lithium-enolate Claisen rearrangements can be successfully mediated by palladium catalysis so that they smoothly occur even at –78 °C. The reaction has been shown not to follow a concerted, [3,3]-sigmatropic route. Instead, a non-concerted, dissoziative mechanism applies. Stereoselective applications of this novel variant of the enolate Claisen rearrangement are going to be developed.

Experimental Section

Procedure for the Palladium-Catalyzed Enolate Claisen Rearrangement of Allyl Phenylacetate 4: A 100-mL two-necked flask was equipped with a magnetic stirrer and charged with $[Pd_2(dba)_3]\cdot CHCl_3$ (25.9 mg; 25 μmol), (*S*)-Cl-MeO-BIPHEP [(*S*)-**6b**] (65.8 mg; 101 μmol) and LiCl (0.51 g; 12 mmol). The flask was closed with a septum, connected to a combined nitrogen/vacuum line, evacuated for 4 h at 25 °C in order to remove traces of water from the lithium salt, and filled with nitrogen. To this flask was added dry THF (30 mL) and the resulting solution was cooled down to –78 °C. A 100-mL two-necked flask was equipped with a magnetic stirrer, a connection to the combined nitrogen/vacuum line and a resistance low-temperature thermometer that was introduced through the septum. The flask was evacuated and refilled with nitrogen three times. Into this flask diisopropylamine (0.7 mL; 5.0 mmol) and 40 mL of dry THF were injected. After cooling to –78 °C, a 1.6 M solution of butyllithium in *n*-hexane (3.1 mL; 5.0 mmol) was added dropwise by syringe, while keeping the temperature below –70 °C. After stirring at 0 °C for 30 min, the mixture was cooled again to –78 °C and a solution of allyl phenylacetate **4** (0.85 mL; 5.0 mmol) in 5 mL of dry THF was injected by syringe. In the course of the addition, the internal temperature of the solution was not allowed to exceed –70 °C. This solution was stirred for 1 h at –78 °C and then transferred through a cannula into the first flask, which was cooled also to –78 °C. After stirring at –78 °C for 40 h, the mixture was poured into a saturated solution of ammonium chloride (100 mL) and acidified with 2 N sulfuric acid. The aqueous layer was extracted three times with 50-mL portions of diethyl ether. Then the combined organic layers were ex-

tracted with 75 mL of a 20% aqueous solution of potassium carbonate. Thereafter, the aqueous layer was acidified with 6 N sulfuric acid to pH = 1–2 and re-extracted with diethyl ether (3 × 50 mL). The resulting combined organic layer was dried with magnesium sulfate, filtered, and concentrated under reduce pressure. The resulting yellow crude product, which contained the acid **7** in 75% yield according to GC analysis, was purified by chromatography on silica gel to afford an analytically pure sample of (*S*)-2-phenyl-4-pentenoic **7** acid as white solid. R_f = 0.42 (*n*-hexane/ethyl acetate, 3:1 and a few drops acetic acid). $[a]_D^{25}$ = +24 (*c* = 1, acetone) [Lit.[16] + 102.5 for (*S*)-**7**]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.5–2.6 (m, 1 H, 3-H), 2.8–2.9 (m, 1 H, 3-H), 3.6 (t, $^3J_{H,H}$ = 7.7 Hz, 1 H, 2-H), 5.0 (d, $^3J_{H,H}$ = 10.4 Hz, 1 H, *cis* 5-H), 5.1 (d, $^3J_{H,H}$ = 17.0 Hz, 1 H, *trans* 5-H), 5.7–5.8 (m, 1 H, 4-H), 7.3–7.4 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz. $CDCl_3$): δ = 37.5, 51.7, 117.7, 128.0, 128.5, 129.1, 135.3, 138.2, 179.6 ppm. GC column: DN-GAMMA 25 m × 0.25 mm × 0.25 µ, column temperature 85 °C, flow 1.5 mL/min [(*S*)-**7** t_R = 52.03 min, (*R*)-**7** t_R = 53.29 min].

Mass spectrometric data were obtained from a Finnigan MAT 95 double focusing sector field instrument applying electron ionization at 70 eV, while GC/MS measurements were performed using a Finnigan MAT SSQ 7000 single quadrupole MS connected to a Trace GC. Calculations of isotopic distributions were performed using MassLib software package (MSP Kofel, Zollikofen, Switzerland).

Acknowledgments

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[21] A referee of this article suggested an alternative mechanism assuming a reaction of the ester enolate **5** with allyl complex **13** to give the ester **12**. The formation of pentenoic acid **7** is explained as a palladium mediated cleavage of the allyl ester that, in turn, regenerates the allyl complex **13**. Although this route cannot be excluded, we consider our mechanism to be the more plausible one. First, the conditions usually used for the deprotection of allylic esters by palladium catalysis require at least room temperature and the presence of stronger nucleophiles. In addition, we have shown that doubly deprotonated carboxylic acids like **16** can be allylated directly in palladium catalysis. Thus, it seems to be plausible that such dianions are the common intermediates in the direct allylation and the Claisen rearrangement. Both reactions lead to the same stereochemical outcome giving predominantly the (*S*) enantiomer of the acid **7** when mediated with ligand (*S*)-**6**.

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