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Memory and dynamics in Pd-catalyzed allylic alkylation with P,N-ligands

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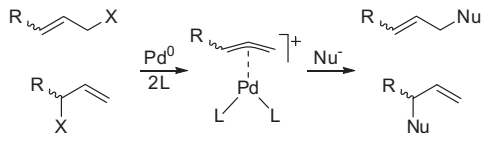
Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

The memory effect, known to exert a strong influence on selectivity in some applications of the Pd-catalyzed allylic alkylation, has been investigated for a catalytic system based on a bidentate P,N-ligand. Although this system might be expected to show strong memory effects due to the difference in the *trans* influence of the two donor atoms (P > N), isotopic labeling revealed an almost complete absence of regioretention. Modeling of dynamic processes in the intermediate (η^3-allyl)Pd complex allowed this observation to be rationalized in terms of anion-assisted apparent rotation. The study has allowed seemingly conflicting reports on the behavior of (η^3-allyl)Pd systems to be unified by a computational model.

1. Introduction

Palladium-assisted allylic alkylation, often termed as the Tsuji–Trost reaction, is a well-explored process and is frequently applied in organic synthesis.[1] In the Tsuji–Trost reaction, isomeric starting materials give rise to the same set of products, since the reaction proceeds, in principle, via a common intermediate (Scheme 1). The product distribution is influenced by the allyl substituents and by the ligands (L) that are used. Although there is a strong, substrate-dependent preference for certain motifs, for example, a conjugated *E*-configured double bond in the product, significant selectivity can still be achieved via the appropriate matching of substrates with ligands.[2,3] In particular, the asymmetric allylic alkylation (AAA) has been very successful,[4] especially for substrates that proceed via symmetric 1,3-disubstituted (η^3-allyl)Pd intermediates.[5–7]



Scheme 1. Pd-assisted allylic alkylation.

In some cases, it has been found that the product distribution is dependent on the substrate used, even when two substrates should proceed through a common intermediate, as outlined in Scheme 1. This phenomenon is generally termed a 'memory effect',[8] and can be seen as a propensity for the product to retain the chirality,[9] regiochemistry,[10] or double bond geometry[2,11] of the substrate. The underlying mechanism of the memory effect has been studied, and been found to result from the fact that different substrates yield different isomeric forms of the (η^3-allyl)Pd intermediate. When all such isomers are in rapid equilibrium and nucleophilic attack is slow (Curtin–Hammett conditions), there is no memory effect, and isomeric substrates do indeed give identical product distributions. However, if the dynamic processes in (η^3-allyl)Pd complexes[12] are slow, relative to the nucleophilic attack,[13] then the reactions can display substantial regio- and stereo-retention, that is, powerful memory effects (Scheme 2).[11,13,14]

When the intermediate is an unsymmetrically 1,3-disubstituted allyl, the dynamics occur in two mirror image manifolds that can crossover, possibly via Pd(0)-catalysis[15,16] (Scheme 2). However, in most cases this process is either very slow or undetectable relative to the net catalytic flux within the individual manifolds. Pairs of substrates related by the simultaneous inversion of both the allylic and alkenyl configurations (e.g., *R,E*- and *S,Z*-) belong to the same manifold, and the enantiomeric pair to the other. The fast dynamic equilibration within a manifold and the very slow crossover into the complementary manifold was recently utilized as part of an enantioconvergent procedure, where both enantiomers of a racemic starting material selectively, and without separation, furnished one enantiomer of an intermediate in a total synthesis of the natural products pyranicin and pyragonicin.[17,18]

The isomerization process illustrated in Scheme 2 is an η^3–η^1 process, sometimes referred to as 'π–σ–π', or '*syn–anti*', isomerization. Compared to the initial (η^3-allyl)Pd complex, the (η^1-allyl)Pd isomer has an additional coordination site available for the coordination of an additional ligand, either the counter-ion or a ligand from solution, during or after the η^3- to η^1-isomerization. The formation of (η^1-allyl)Pd intermediates and the rate of *syn–anti* isomerization is therefore accelerated by ligands in solution, in particular by anions such as halides or carboxylates.[12] In addition,

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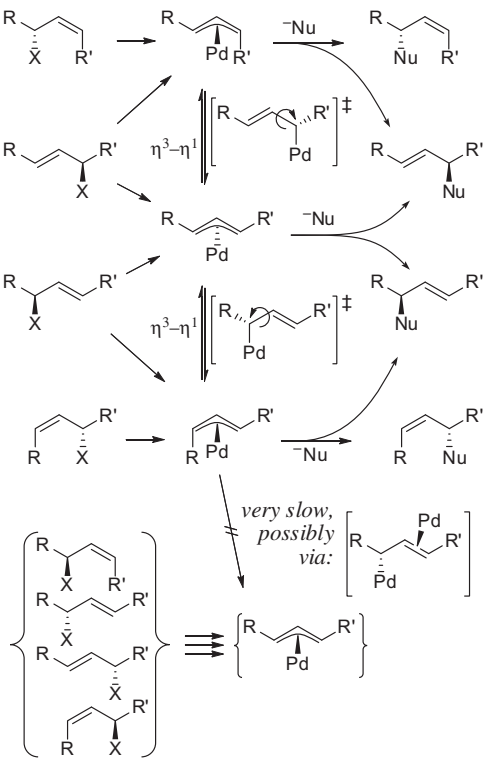
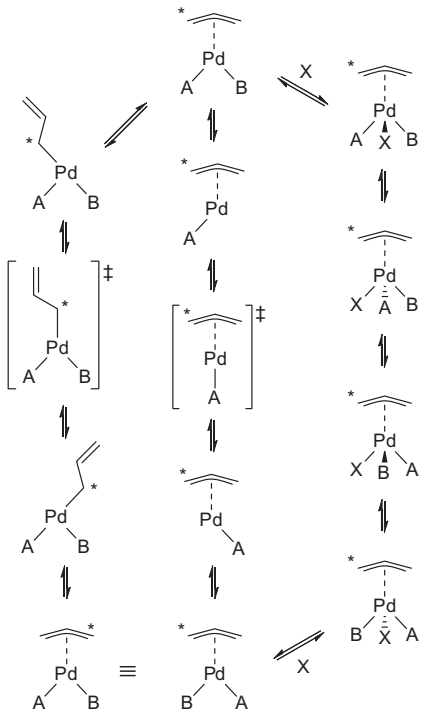


Scheme 2. Two dynamic manifolds of (η^3-allyl)Pd isomerization.

there is an apparent rotation or '*syn–syn*, *anti–anti*' isomerization, which exchanges the position of the two ligands (L) in the square plane, relative to the η^3-allyl moiety. Several underlying processes have been proposed for this observed exchange (Scheme 3). A simple allyl rotation has been considered improbable, since Pd^{II} complexes have a strong preference for the square planar geometry, but (η^1-allyl)Pd could potentially undergo positional isomerization (Scheme 3, left). Likewise, ligand dissociation has been demonstrated,[19] and the remaining ligand could then shift position via a T-shaped transition state or intermediate (Scheme 3, center). Finally, the observation that the process is strongly accelerated by chloride ions has led to the proposal of rapid Berry pseudorotation in a pentacoordinate complex as the major contributor to the apparent rotation (Scheme 3, right).[20]



Scheme 3. Three mechanisms for apparent rotation in (η^3-allyl)Pd complexes: left hand side, η^3–η^1-isomerization; center, ligand (B) dissociation allowing access to a T-shaped complex; right hand side, ligand (X, e.g., counter-ion) association allowing Berry pseudorotation.

Returning to the asymmetric allylic alkylation (AAA), the reaction is generally employed with substrates that generate a symmetric 1,3-disubstituted (η^3-allyl)Pd complex. In such systems, the enantioselectivity arises from the ability of the ligand to direct the nucleophile to one specific allyl terminus. This can be achieved, for example, by directing the nucleophile via hydrogen bonding[21,22] or by employing an electronically dissymmetric ligand with a strong *trans* effect difference, like the highly effective P,N-ligands.[23–26] In the latter case, it is expected that during the generation of the η^3-allyl intermediate from the η^2-alkenyl precursor, the strong *trans* influence of the phosphorous will result in the expulsion of the leaving group (X) when the alkene is orientated such that X is *trans* to P. Ionization, followed by nucleophilic attack, without isomerization, would then lead to a strong region-retention as the nucleophile would, again, be directed by the *trans* influence of P. When the stereoselectivity is dependent on an induced regioselectivity, as is the case with η^3-cycloalkenyl or η^3-1, 3-diphenylallyl complexes, regio-retention will have a deleterious effect on the stereoselectivity, albeit only at higher conversions if there is a significant degree of kinetic resolution of the substrate.[10] Despite this, the P,N-systems give fast and selective reactions, and thus do not seem to suffer from memory effects. In stark contrast, we have previously shown[11,27] that P,Cl systems afford as much as 40% regio-retention,[‡] despite there being a much smaller difference in the *trans* effect and substantially slower reactions where one would expect the dynamics outlined in Scheme 3 to facilitate full equilibration and negate any opportunity for memory.

To address this conundrum, we have undertaken a combined experimental and computational study of memory effects in catalytic systems with P,N-ligands. We want to ensure that our results are not complicated by kinetic resolution of enantiomeric substrates,[10] and have therefore elected to work with a non-chiral P,N-ligand, $Ph_2P–CH_2CH_2–NMe_2$ **5** which can be viewed as a chimeric combination of two frequently employed non-chiral palladium ligands, dppe and TMEDA.

2. Results and discussion

The above-mentioned analysis centers around the *trans* effect, and we first wanted to verify the expectation that this would favor nucleophilic attack *trans* to phosphorus, a key aspect of the mechanism for asymmetric induction by chiral P,N-ligands.[28] We addressed this question computationally by calculating the approximate transition states for attack by a sodium dimethyl malonate nucleophile at the two termini of a simple (η^3-allyl)Pd complex bearing the ligand **5** that was employed experimentally (Fig. 1). As expected, the attack *trans* to the phosphorus is favored, by ca. 7 kJ/mol. At room temperature, this energy difference corresponds to about an order of magnitude in reactivity difference.

Experimental studies were then carried out with labeled acyclic allylic substrates **1a–c**, synthesized from acryloyl chloride, and the

[‡] We have used a definition of stereo- and regio-retention similar to that of enantioselectivity, that is, the excess of the isomer showing retention. Thus, if the ratio between isomers A and B is expected to be 1 in the absence of memory effect, and B is favored by memory, the retention is $100\% * (1 - A/B)/(1 + A/B)$.

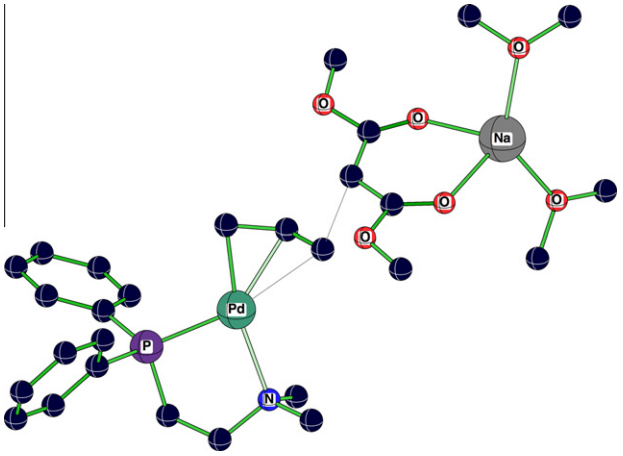
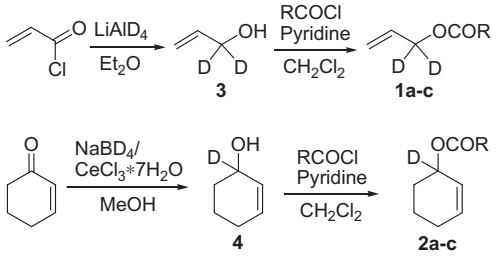


Figure 1. Preferred nucleophilic attack at a (η^3-allyl)Pd complex with a P,N-ligand.

corresponding labeled cyclic substrates **2a**–**c**, synthesized from 2-cyclohexenone, as depicted in Scheme 4.



Scheme 4. Preparation of labeled substrates to test for memory effects in allylic alkylation.

Initial allylic alkylations were performed using 5 mol % of ligand **5** and 2.5 mol % of $Pd_2(dba)_3$ to give a 1:1 ligand/Pd^0 pre-catalyst; the reactions were run at room temperature for 20 h under nitrogen atmosphere, (Chart 1). Sodium diethyl methylmalonate was used as the nucleophile. No significant regio-retention was observed for any of the substrates (Table 1, entries 1–6).

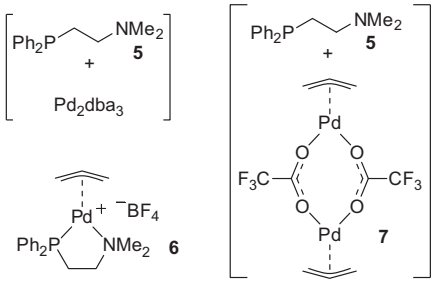


Chart 1. Pre-catalyst complexes.

Amatore and Jutand have shown that dba (*E*-dibenzylidene acetone) undergoes equilibrium complexation with $[Pd^0(PPh_3)_2]$ to generate $[Pd^0(dba)(PPh_3)_2]$.[29] Since the pre-catalyst liberates dba, it is possible that that an analogous coordination affects our results. To exclude this possibility, we prepared two alternative pre-catalyst complexes, [(η^3-allyl)Pd·**5**]BF_4 **6** and [(η^3-allyl)PdO$COCF_3$]$_2$ **7**, Chart 1.

The amount of catalyst was reduced to 2 mol % in order to minimize the amount of diethyl allylmethylmalonate **8** formed from the pre-catalyst activation event. The reaction showed regio-retention for all the substrates (entries 7–15 in Table 1) confirming that

Table 1
Results from the allylic alkylation of **1a**–**c** and **2a**–**c** by NaC(Me)$(CO_2Et)_2$ using Pd complexes of ligand **5**

Entry	Substrate	Pre-catalyst	Retention[§] (%)
1	**1a**	**5** + Pd_2dba_3	−2[a]
2	**1b**	**5** + Pd_2dba_3	0[a]
3	**1c**	**5** + Pd_2dba_3	−2[a]
4	**2a**	**5** + Pd_2dba_3	2
5	**2b**	**5** + Pd_2dba_3	0
6	**2c**	**5** + Pd_2dba_3	3
7	**1a**	**6**	14
8	**1b**	**6**	17
9	**1c**	**6**	8
10	**2a**	**6**	10
11	**2b**	**6**	5
12	**2c**	**6**	6
13	**2a**	**5** + **7**	9
14	**2b**	**5** + **7**	1
15	**2c**	**5** + **7**	7

[a] The memory effect should be a positive number. Small negative numbers arise from minor errors in the integration of ^{1}H NMR signals.

dba is not an innocent spectator ligand, although the magnitude of the effect is small.

The partial regio-retention in the reaction when using **6** or **7** as pre-catalysts presumably arises from the rate of the dynamic processes (Scheme 3), such as η^3–η^1-isomerization and ligand rotation via Berry pseudorotation induced by CF_3COO^- anion coordination, being only slightly slower than nucleophilic attack of the malonate on the allyl.

2.1. Isomerization/rearrangement of starting allyls

The deuterium labeling strategy (Scheme 4) is based on the isotope acting simply as a marker for the carbon that originally bore the leaving group 'X'. It is thus essential that the substrate does not undergo isomerization prior to reaction. In one of the experiments, substrate **2c** was recovered and it was found to have undergone complete equilibration; under such circumstances, no regio-retention would be detected irrespective of whether the alkylation reaction was proceeding with regio-retention or not. To confirm if the rearrangement of allylic substrates occurs under these conditions, a series of experiments were performed in which the reaction was assembled without the addition of the nucleophile (Table 2). After 65 h, the reaction was quenched and the mixture was analyzed by ^{1}H NMR spectroscopy. All substrates **1a**–**c**, **2b**–**c**, except for cyclohexenyl acetate **2a**, led to full regio-isotopomeric equilibration of the allyl moiety, when using $Pd_2(dba)_3$ as a

Table 2
Results from the isomerization experiments

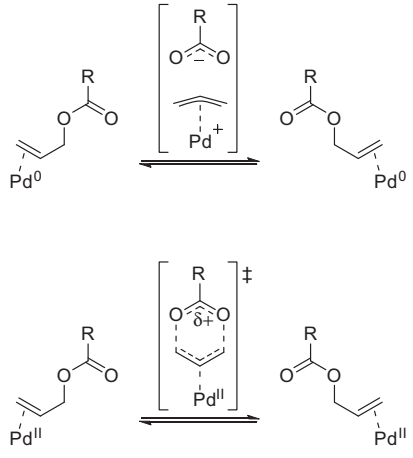
Entry	Substrate	Catalyst	Isomerized allyl
1	**1a**	**5** + Pd_2dba_3	Yes
2	**1b**	**5** + Pd_2dba_3	Yes
3	**1c**	**5** + Pd_2dba_3	Yes
4	**2a**	**5** + Pd_2dba_3	No
5	**2b**	**5** + Pd_2dba_3	Yes
6	**2c**	**5** + Pd_2dba_3	Yes
7	**2a**	**6**	No
8	**2b**	**6**	No
9	**2c**	**6**	No
10	**2a**	**6** + 0.05 equiv Nu^-	No
11	**2b**	**6** + 0.05 equiv Nu^-	No
12	**2c**	**6** + 0.05 equiv Nu^-	No
13	**2a**	**5** + **7**	No
14	**2b**	**5** + **7**	No
15	**2c**	**5** + **7**	No
16	**2a**	**5** + **7** + 0.1 equiv Nu^-	'Slight'
17	**2b**	**5** + **7** + 0.1 equiv Nu^-	'Slight'
18	**2c**	**5** + **7** + 0.1 equiv Nu^-	'Slight'

palladium source (Table 1, entries 1–6), but no equilibration of any of the allyls was observed when using pre-catalysts **6** or **7** (Table 2, entries 7–9 and 13–15). This suggested that Pd(0) was responsible for the equilibration (via reversible ionization of the leaving group). To test this, we conducted another series of experiments using **6** or **7**, but this time added 5 and 10 mol %, respectively, of sodium diethyl methylmalonate in order to alkylate the pre-catalyst and generate Pd(0). However, after 20 h, no equilibration was observed when using **6** (Table 1, entries 10–12) and only a minor extent (5–10%) of equilibration of all the allyls was observed when using **7** (Table 1, entries 16–18), that is, there is no sufficient equilibration to explain the low regio-retention in the reaction. By contrast, the small amount of alkylation product **9** formed in the reaction when using **7** showed no measurable regioselectivity for any of the substrates. These results strongly suggest that it is not equilibration of the allylic substrate prior to its alkylation that is responsible for the low regio-retention in the reaction when using **7** as a pre-catalyst.

2.2. Isomerization mechanism

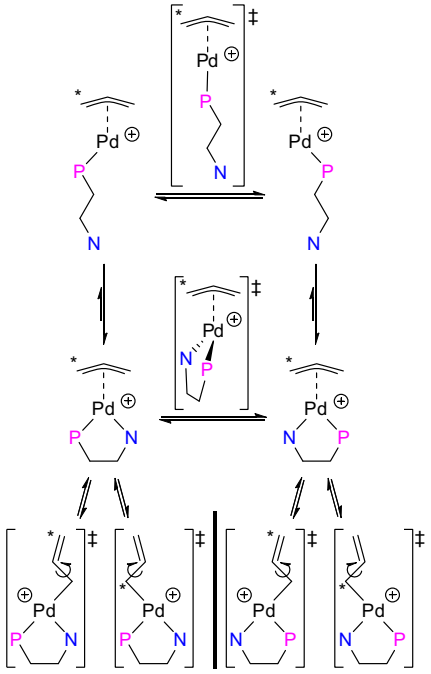
We became interested in the mechanism for the equilibration of **2b** and **2c** with their regio-isotopomers. The isomerization of allyls has been the subject of several investigations, but mainly concerns the stereochemical aspects of the process.[30–32]

In order to examine whether the return of the leaving group was internal or external, a crossover experiment was performed. Cyclohexenyl carbonate and allyl benzoate were mixed, and then a catalyst generated from 5 mol % of **5** and 2.5 mol % of $Pd_2(dba)_3$ was added. A detailed analysis of the reaction mixture by GC–MS showed that neither crossover product (cyclohexenyl benzoate and allyl carbonate) was detectable in the reaction mixture after 1 h or indeed after 70 h reaction time; strongly pointing to an intramolecular or internal ion pair isomerization mechanism. A plausible explanation for this observation is that benzoate and carbonate groups can stabilize the 1,3-oxo cyclohexenyl cation in the transition state, thus leading to a Pd(II)-catalyzed 1,3-migration, similar to the Overman rearrangement[33] (Scheme 5). This process would be expected to be less favorable for acetates, as observed in the isomerization/rearrangement experiment, where the acetate did not return to the allyl (entry 4 in Table 2).



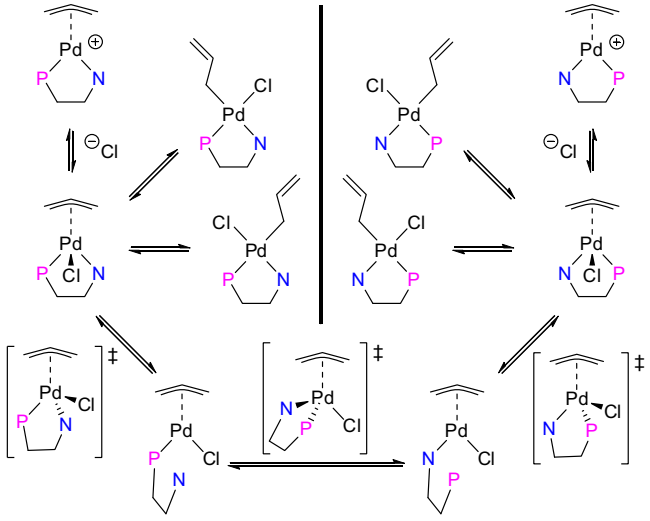
Scheme 5. Plausible Pd(0)- and Pd(II)-assisted pathways for isomerization of allyl substrates.

From the very minor memory effects observed in the experimental studies, it is clear that the chemical information encoded in the initially formed (η^3-allyl)Pd complex is scrambled before nucleophilic attack, presumably through apparent rotation. To aid in the resolution of the long-standing controversy regarding this process, we initiated a computational study of plausible dynamic processes in cationic (η^3-allyl)Pd complexes with a model P,N-ligand (Scheme 6).



Scheme 6. Plausible dynamic processes in (η^3-allyl)Pd complexes with P,N-ligands.

As expected, the nitrogen atom could be dissociated,[19] and the resulting complex isomerized through a T-shaped transition state; however, the (η^1-allyl)Pd complex turned out to be a transition state for bond rotation, not a stable structure. Since a transition state cannot itself go through another process, the (η^1-allyl)Pd complex cannot engage in the apparent rotation process that leads to positional isomerization. Attempts to locate such a reaction path instead yielded a skewed (η^3-allyl)Pd complex corresponding to unsymmetrical rotation of the η^3-allyl. This η^3-allyl structure is in fact the lowest energy path for apparent rotation in the cationic complex, with a free energy barrier of 113 kJ/mol.



Scheme 7. Chloride-assisted dynamic processes in (η^3-allyl)Pd complexes with P,N-ligands.

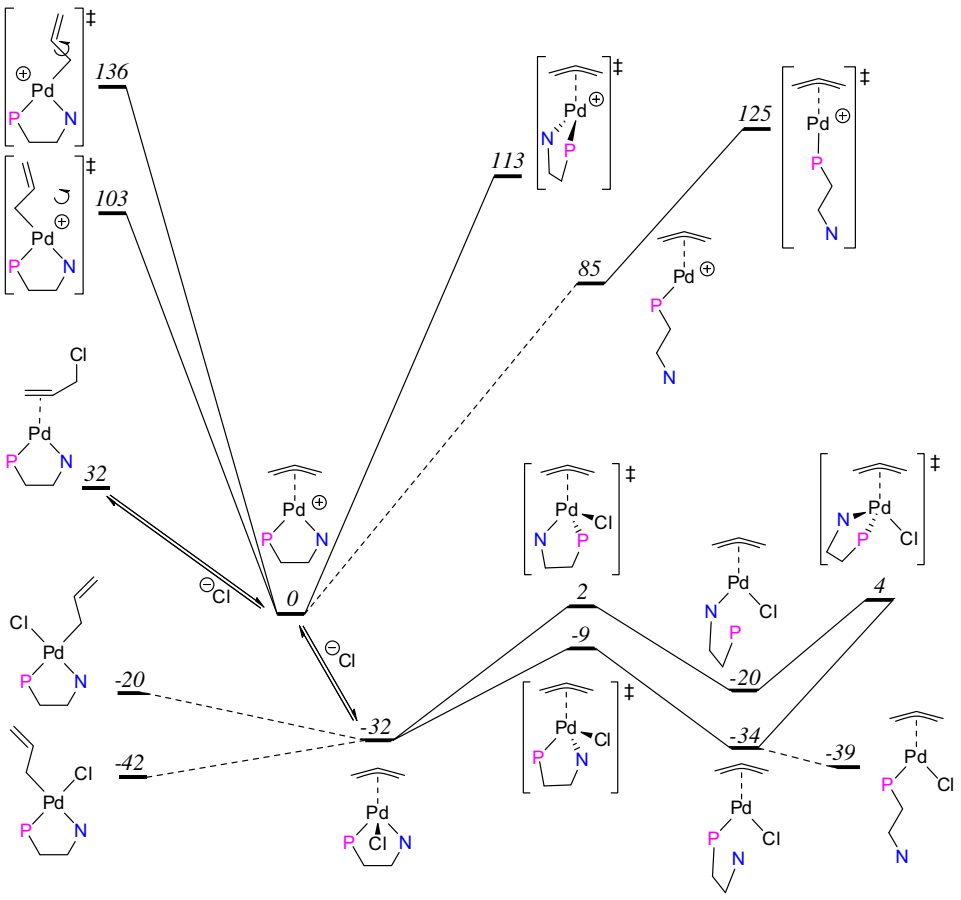
We also investigated the effect of added anionic ligands modeled by a chloride anion (Scheme 7). There are no ground state structures corresponding to trigonal bipyramids. All the stable structures are square planar, with the last ligand loosely associated outside the coordination plane, but not coordinated to Pd. This is, in some ways, expected behavior, since there are no low-lying orbitals on Pd that are able to accept electron pairs from outside the coordination plane. An X-ray structure of a presumed pentacoordinate (η^3-allyl)Pd complex with phenanthroline and chloride[20] does in fact corresponds to the computed structures seen here; on close inspection, it is clear that one nitrogen is rigidly held by the ligand framework, such that it is at a distance that corresponds to a non-bonded interaction, not coordination. The transition states corresponding to Berry pseudorotation exist, but the structures connected by these paths are not pentacoordinate. Thus, these 18-electron transition states correspond to the 10-electron structure in the S_N2 reaction; they are in fact transition states for ligand exchange. This is in qualitative agreement with the view on bonding in transition metal complexes reported by Landis and Weinhold.[34]

The (η^1-allyl)Pd complexes are stable, square planar structures when coordinated with a chloride ligand (Scheme 7). This is in agreement with the observation that *syn–anti* isomerization is strongly accelerated by chloride, but also shows that this process cannot be responsible for the apparent rotation, since no positional isomerization is possible in this square planar complex. Thus, the only chloride-accelerated process corresponding to an overall apparent rotation is the series of pseudo-rotation-like ligand replacement processes shown in the bottom of Scheme 7.

In addition to the dynamic processes within the Pd-allyl manifold, it has also been shown that the leaving group can re-enter,[30] or in other words, that the initial ionization in the catalytic cycle is reversible. With two phosphine ligands (bidentate or bis-monodentate), the equilibrium has been shown to lie on the side of the Pd^0/allyl carboxylate side.[35] If the re-entry is fast relative to the nucleophilic attack, as has been implied with bidentate phosphines,[22,30] Curtin–Hammett considerations would apply, and thus the geometries and energies of Pd-allyl intermediates would lose their ability to cause a memory effect.

The full free energy surface of these processes is shown in Scheme 8. As can be seen, chloride coordination is strongly favored, which is in agreement with the experimental observations of a tight ion pair.[32] However, the energy gain on association may be overestimated due to approximations in the computational model. In any case, it is clear that isomerization barriers are very low in the presence of anionic ligands such as chloride. Even the small amount of comparatively weak acetate ligand present in the catalytic reactions will be able to catalyze the apparent rotation, which is in perfect agreement with the observation of a very low memory effect in the experimental system. The lowest energy states correspond to a complex with dissociated nitrogen ligand at −39 kJ/mol, reminiscent of a previously determined X-ray structure,[20] and an (η^1-allyl)Pd complex at −42 kJ/mol, in good agreement with observations by Amatore and Jutand in systems with phosphine ligands.[36]

The Pd^0/allyl chloride complex at 32 kJ/mol is worthy of note. From the energies, it is clear that formation of this complex can be neglected compared to other chloride-catalyzed processes. However, this is not necessarily true for carboxylates. The relative leaving group ability of chloride and acetate is correlated with their pK_{aH} values, differing by ca. 12. This corresponds to a stability difference of ca. 70 kJ/mol at ambient temperature. The difference



Scheme 8. Free energies of isomerization processes in Pd-allyl complexes.

should be smaller in this system, since the comparison is being made between a covalently attached ligand with a coordinated, not free, leaving group; nonetheless, it is still plausible that the Pd^0/allyl carboxylate complex could become significant, or even the resting state.[35]

3. Conclusion

The expected regio-retention in allylic alkylations with deliberately simple P,N-ligands could be detected experimentally, but only to a very low extent, and not when using a pre-catalyst containing dba. The presence of coordinating anions, such as the leaving group, suppresses the memory effect. This is a strong indication that the apparent rotation is fast compared to nucleophilic attack for the intermediate (η^3-allyl)Pd complex, and that the apparent rotation is catalyzed by anionic ligands in solution, in good agreement with the literature data.[12]

The computational study has identified intermediates and interconversion paths relevant to the observations. In general, dynamic processes are slow in cationic complexes with non-coordinating counter-ions. The lowest barriers for *syn–anti* exchange and apparent rotation are ca. 103 kJ/mol and 113 kJ/mol, respectively. These two processes are independent, with no mechanistic connection. The apparent rotation is most reminiscent of a barrier-less ligand dissociation followed by an S_N2-like ligand substitution, P replacing N or vice versa, at one coordination site in the square plane.

In the presence of a coordinating anion (here modeled by chloride), dynamic processes are strongly accelerated, sufficient to fully scramble the regiochemical memory in the (η^3-allyl)Pd complex. The most likely process for the apparent rotation is an associative ligand replacement, with transition states highly reminiscent of Berry pseudorotation, but connecting square planar structures with loosely associated fifth ligands, not true pentacoordinated complexes. *syn–anti* Exchange via square planar (η^1-allyl)Pd complexes is also a very fast process, but again without a mechanistic connection to the apparent rotation. Finally, nucleophilic attack of the leaving group, leading to reversibility of the initial ionization step, can also be a favored process. Even with the chloride model used here, the (η^2-chloropropene)Pd^0 complex is only 74 kJ/mol above the most stable Pd^{II} complex, a relatively low energy compared to the barriers of >100 kJ/mol for the dynamic processes in the free, cationic (η^3-allyl)Pd complexes. For carboxylates that can form strong C–O bonds, the energy difference is expected to be much smaller, may be even disappearing.[35]

The reversibility of the initial ionization could also help rationalize the starting material racemization observed. However, as evidenced by lack of leaving group exchange in crossover experiments, other pathways must also be active for this process. We speculate that a Pd^{II}-catalyzed Overman rearrangement could rationalize our observations (Scheme 5).

4. Experimental

4.1. General

All reactions were performed in oven-dried glassware and under a nitrogen atmosphere, except for the synthesis of cyclohexenol. Solvents were distilled prior to use. THF was distilled from Na/benzophenone, CH_2Cl_2, and pyridine from CaH_2, under a nitrogen atmosphere. Et_2O was purchased as anhydrous and stored over molecular sieves (4 Å). Commercially available reagents were used as delivered unless stated otherwise. TLC was performed using alumina plates coated with Silica Gel 60, F_{254}. The plates were visualized by using a mixture of 2% $KMnO_4$ and 4% K_2CO_3 (aq) followed by warming with a heat-gun. Column chromatography was performed using Silica Gel 60, 0.04–0.06 mm.

Products were identified by NMR spectroscopy. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz Varian instrument and a JEOL Eclipse 400 instrument, operating at 400 MHz for ^1H nuclei. Samples were dissolved in $CDCl_3$ and chemical shifts are given in (parts per million) ppm relative to residual $CHCl_3$ (7.27 ppm). Substrates were synthesized using modified literature procedures.

4.1.1. Allyl alcohol-1-D_2 3[37]

At first, $LiAlD_4$ (262 mg, 6.25 mmol) was added to dry Et_2O (15 ml) at 0 °C. The solution was flushed with N_2 and then cooled to 0 °C in an ice-bath. Acryloyl chloride (813 μl, 10 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h. The reaction was then quenched with H_2O (260 μl), NaOH (15%, 260 μl), and H_2O (790 μl), and then stirred at room temperature for 30 min. The white precipitate was filtered off and washed with Et_2O (2–3 ml). The solution was dried with $MgSO_4$, filtered through a glass filter funnel, and the solvent was distilled off, yielding the crude product as a yellow oil. The crude product was used directly without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.99 (m, 1H), 5.27 (m, 1H), 5.14 (m, 1H).

4.1.2. Cyclohexenol-1-D 4[38]

Cyclohexenone (2.42 ml, 25 mmol) was added to a solution of $CeCl_3{\cdot}7H_2O$ (9.3 g, 25 mmol) in methanol (20 ml). After cooling to 0 °C, $NaBD_4$ (1.0 g, 25 mmol) was added in portions over a period of 5 min. The solution was stirred at 0 °C for 20 min. The reaction was quenched with HCl (1 M, 30 ml), and the product was extracted with Et_2O (3 × 20 ml), washed with brine (15 ml), then dried over $MgSO_4$, and yielded the pure product after evaporation of the solvent, as a clear oil (2.2 g, 90%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.84 (m, 1H), 5.75 (m, 1H), 1.54–2.19 (m, 6H).

4.2. Synthesis of allylic acetates[11]

4.2.1. Compound 1a

Acetyl chloride (570 μl, 8.0 mmol) and pyridine (645 μl, dry, 8.0 mmol) were added in portions to a cooled solution of **3** (0.36 g, 6 mmol) in CH_2Cl_2 (15 ml, dry) at 0 °C. A white precipitate formed almost immediately. The reaction mixture was allowed to reach room temperature during 20 h. The reaction mixture was cooled again and the precipitate formed was filtered off and washed with CH_2Cl_2. The solution was washed with ice-water (10 ml), ice-cooled brine (15 ml), dried with Na_2SO_4, and yielded a yellow oil after *careful* evaporation. The residue was distilled, by using a Hickmann apparatus, collecting the product at 101–104 °C (222 mg, 2.2 mmol, 35%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.86–5.95 (m, 1H), 5.28–5.35 (m, 1H), 5.23 (m, 1H), 4.59 (m, 2H) absent when D, 2.08 (s, 3H).

4.2.2. Compound 2a

Acetyl chloride (1.10 ml, 15 mmol) and pyridine (1.20 ml, dry, 15 mmol) were added in portions to a cooled solution of **4** (0.99 g, 10 mmol) in dry CH_2Cl_2 (15 ml), at 0 °C. A white precipitate formed almost immediately. The reaction mixture was allowed to reach room temperature during 20 h, and the reaction was then quenched with NH_4Cl (aq satd, 20 ml). The product was extracted with CH_2Cl_2 (2 × 25 ml), washed with aq. saturated $NaHCO_3$ (25 ml), brine (25 ml), and then dried with $MgSO_4$, yielding the crude product as a yellow oil after evaporation of solvent. The crude product was purified by column chromatography (EtOAc/pentane, 1:9), yielding the product as a clear oil (0.85 g, 6.0 mmol, 60%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.95 (m, 1H), 5.68 (m, 1H), 5.24 (m, 1H) absent when D, 1.55–2.10 (m, 9H).

4.3. General procedure for the synthesis of allylic benzoates

Pyridine (970 μl, 12 mmol) and benzoyl chloride (1.40 ml, 12 mmol) were added in portions to a solution of allylic alcohol **1** or **2** (10 mmol) in dry CH_2Cl_2 (15 ml) at 0 °C. The solution was allowed to reach room temperature and was stirred for 20 h. The reaction mixture was filtered through basic alumina into a separation funnel and washed with H_2O (20 ml) and brine (20 ml), then dried with $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography (EtOAc/pentane, 1:4), yielding the product as a clear oil (1.2 g, 67%, for cyclohexenyl benzoate). ^{1}H NMR (400 MHz, $CDCl_3$): **1b** δ (ppm) 8.08 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 5.98–6.08 (m, 1H), 5.38–5.98 (m, 1H), 5.29 (m, 1H), 4,84 (m, 2H) absent when D. **2b** δ (ppm) 8.08 (m, 2H), 7.55 (m, 1H), 7.42 (m, 2H), 6.01 (m, 1H), 5.83 (m, 1H), 5.51 (m, 1H) absent when D, 1.55–2.18 (m, 6H).

4.4. General procedure for the synthesis of allylic carbonates[39]

Pyridine (806 μl, 10 mmol) was added to a cooled solution of cyclohexenol (0.78 g, 8 mmol) in CH_2Cl_2 (15 ml). Thereafter methyl chloroformate (770 μl, 10 mmol) was added dropwise, and a white precipitate started to form. The stirred solution was allowed to reach room temperature during 17 h. H_2O (15 ml) was added and the product was extracted with CH_2Cl_2 (3 × 20 ml). The organic phase was washed with 1 M HCl (2 × 20 ml), H_2O (15 ml), and brine (15 ml). Thereafter the reaction was dried with $MgSO_4$, and after evaporation of the solvent, the crude product was purified by column chromatography (EtOAc/pentane, 1:9), yielding the product as a clear oil (0.45 g, 2.9 mmol, 36%). ^{1}H NMR (400 MHz, $CDCl_3$): **1c** δ (ppm) 5.88–6.00 (m, 1H), δ 5.36 (m, 1H), δ 5.28 (m, 1H), δ 4.63 (m, 1H) absent when D, 3.80 (s, 3H). **2c** δ (ppm) 5.97 (m, 1H), 5.75 (m, 1H), 5.11 (m, 1H) absent when D, 3.76 (m, 3H), 1.56–2.12 (m, 6H).

4.4.1. 2-(Diphenylphosphino)-*N*,*N*-dimethylethaneamine 5[40]

Potassium *tert*-butoxide (2.47 g, 22 mmol) was dissolved in dry THF (30 ml) and the solution was flushed with N_2. Diphenylphosphine (1.73 ml, 10 mmol) was added and the orange-red solution was stirred at room temperature for 30 min. Then 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (1.44 g, 10 mmol) was added in one portion and the reaction mixture was refluxed for 20 h. The solvent was evaporated and 10% HCl (25 ml) was added. The acidic phase was washed with Et_2O (25 ml), and then made alkaline with 5 M NaOH. The product was extracted with Et_2O (3 × 25 ml), the organic phase was washed with brine (20 ml), dried with Na_2SO_4, and the crude product was obtained as a cloudy oil after evaporation. The oil was dissolved in a small amount of Et_2O and filtered through a column of basic alumina, yielding the product as a clear oil (0.73 g, 2.8 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40–7.48 (m, 4H), 7.29–7.38 (m, 6H), 2.36–246 (m, 2H), 2.21–2.28 (m, 8H).

4.4.2. Compound [(η^3-allyl)Pd·5]BF_4 6[3]

At first, [(η^3-allyl)PdCl]$_2$ (18.3 mg, 0.05 mmol) in CH_2Cl_2 (1 ml) was added to $AgBF_4$ (20.4 mg, 0.105 mmol), under N_2. A white precipitate was formed almost immediately. The solution was stirred at 20 °C for 15 min. Next, **5** (25.7 mg, 0.10 mmol) was added, whereupon the solution turned brown and was stirred for 1 h. The reaction mixture was filtered through a 2 cm column of Celite in a Pasteur pipette and thereafter the solvent was removed under reduced pressure, yielding the crude product as a beige crystalline solid (44.5 mg, 0.91 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.50–7.70 (m, 10H), 5.85 (m, 1H), 4.84 (m, 1H), 4.02 (m, 1H), 3.90 (m, 1H), 2.98–3.11 (m, 5H).

4.4.3. Compound [(η^3-allyl)PdOCOCF$_3$]$_2$ 7[41]

At first, Pd(dba)$_2$ (57.5 mg, 0.10 mmol) was dissolved in dry THF (0.8 ml) and carefully evacuated, then refilled with N_2 three times. Allyl trifluoroacetate (16.95 mg, 0.11 mmol) was dissolved in dry acetonitrile (0.2 ml) and added to the deep-red Pd(dba)$_2$ solution. The solution became light green after 5 min., and was stirred at room temperature for a further 25 min. The mixture was filtered through a glass filter funnel and the solvents removed in vacuo. The residue was triturated with 10% acetonitrile in H_2O (8 × 1 ml). The extract was filtered and evaporation of the solvent yielded the product as a yellow solid (45 mg, 0.045 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.61 (m, 1H), 4.14 (m, 2H), 3.07 (m, 2H).

4.5. General procedure for the allylic alkylation[11]

At first, NaH (40 mg, 1 mmol, 60% suspension in oil), was dissolved in dry THF (2 ml). Next the flask was evacuated and refilled with N_2. Diethyl methylmalonate (170 μl, 1 mmol) was added dropwise to the suspension, which turned clear after the addition. The solution was stirred at room temperature for 10 min.

Either $Pd_2(dba)_3$ (11.5 mg, 0.0125 mmol) or **7** (6.5 mg, 0.0125 mmol) was dissolved in dry THF (1 ml) and the flask was carefully evacuated and refilled with N_2 three times. Next, **5** (6.2 μl, 0.0250 mmol) was added. The solution was stirred at room temperature for 10 min. Allylic substrate (0.50 mmol) was dissolved in dry THF (1 ml) and added to the Pd-solution, which turned green after a few minutes.

Alternatively, **6** (0.01 mmol, 5 mg) in CH_2Cl_2 (0.1 ml) was added to the allylic substrate (0.50 mmol) in THF (2 ml).

Thereafter the malonate solution was added to the mixture containing allylic substrate and Pd catalyst and was stirred at room temperature for 20 h. The reaction mixture was diluted with Et_2O (5 ml), and washed with 1 M HCl (5 ml), H_2O (5 ml), and brine (5 ml). Thereafter it was dried with Na_2SO_4 and the product mixture was obtained as a yellow oil, after evaporation of solvents. The crude mixture was analyzed without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): **8** δ (ppm) 5.69 (m, 1H), 5.10 (m, 2H), 4.19 (q, 4H), 2.60 (m, 2H), 1.24 (t, 6H). **9** δ (ppm) 5.78 (m, 1H), 5.54 (m, 1H), 4.19 (q, 4H), 3.05 (m, 1H), 1.50–2.20 (m, 6H), 1.32 (s, 3H), 1.45 (t, 6H).

5. Computational details

All DFT calculations were performed in the Jaguar program[¶] using the B3LYP functional[42–44] in conjunction with the LACVP* basis set.[45] Solvent effects were represented by the PBF continuum model[46,47] with default parameters for THF (*solvent = tetrahydrofuran*). Vibrational contributions to the free energy were calculated in the gas phase. No standard state corrections have been applied; energies are appropriate for 1 M concentration of all solvated species. Each order of magnitude reduction in concentration corresponds to a free energy increase of ca. 6 kJ/mol at room temperature.

Transition states for attack of nucleophiles on cationic (η^3-allyl)Pd complexes should be located for the solvated species.[48] However, we have found vibrational contributions to be unreliable for structures optimized with continuum solvation. In addition, the potential energy surface for nucleophilic attack on Pd-allyls in solvent is extremely flat, making the location of true transition states very challenging. We have therefore followed an earlier procedure[22,49] and located approximate transition states by relaxed driving of the coordinate for the forming bond, with full optimization in solvent at each scan point. The full experimental ligand was

[¶] Jaguar v. 7.6 from Schrödinger, Inc., see: http://www.schrodinger.com.

employed, and the nucleophile was represented by dimethyl malonate ion chelating a sodium atom, which was further solvated by two dimethyl ether molecules as THF models.[50] The energies in solvent were compared directly, with the assumption that vibrational contributions and systematic errors in the DFT functional cancel for the very similar structures used in the comparison.[22]

Dynamic processes in (η^3-allyl)Pd complexes were studied using a smaller model system, with H_2P-CH_2CH_2-NH_2 used as a model for the real ligand. This approach will underestimate steric repulsion in the system, but on the other hand, B3LYP is known to overestimate non-bonded repulsive interactions due to the lack of an appropriate treatment of dispersive interactions. The effect of an added chloride was investigated. Chloride is present in small amounts in many catalytic systems and is known to be a highly efficient catalyst for dynamic processes in (η^3-allyl)Pd complexes,[20] but could also be considered a simplified model for other anions like carboxylates that are used as leaving groups and therefore always present. For these complexes, stationary points were determined in gas phase and validated by frequency calculation. Energies in solvent were determined by single point continuum calculations at the optimized geometries. Final free energies were obtained by adding the vibrational contributions (including zero point energies) to the calculated free energies in solvent. This approach is known to exaggerate the entropic contributions and thus favors dissociated species, just like the dispersion error in DFT, but this effect will to some extent be compensated by the choice of small model system.

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