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Memory and dynamics in Pd-catalyzed allylic alkylation with PN-ligands

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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 PN-ligand. Although this system might be expected to show strong memory effects due to the difference in trans influence of the two donor atoms ($P > N$), isotopic labeling revealed an almost complete absence of regioselectivity. 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.

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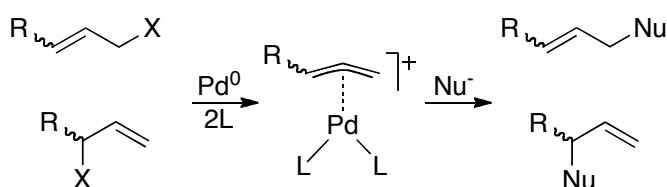
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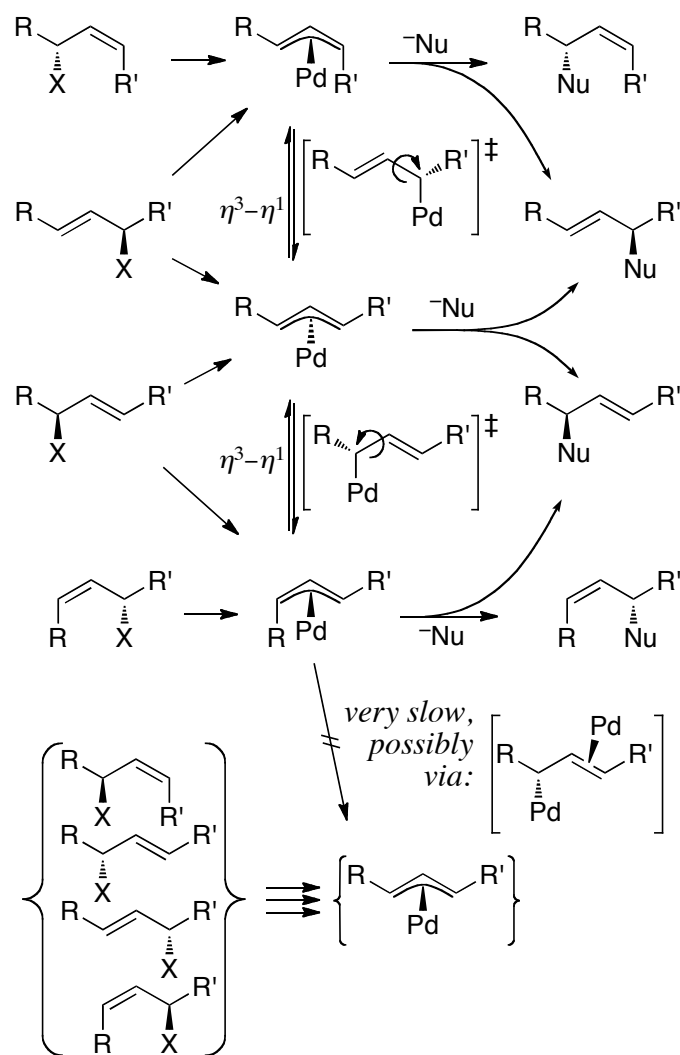
Introduction

Palladium-assisted allylic alkylation, often termed 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 through an 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.^{5,6,7}



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 complexes¹² are slow, relative to nucleophilic attack,¹³ then the reactions can display substantial regio- and stereo-retention, in other words, powerful memory effects (Scheme 2).^{11,13,14}

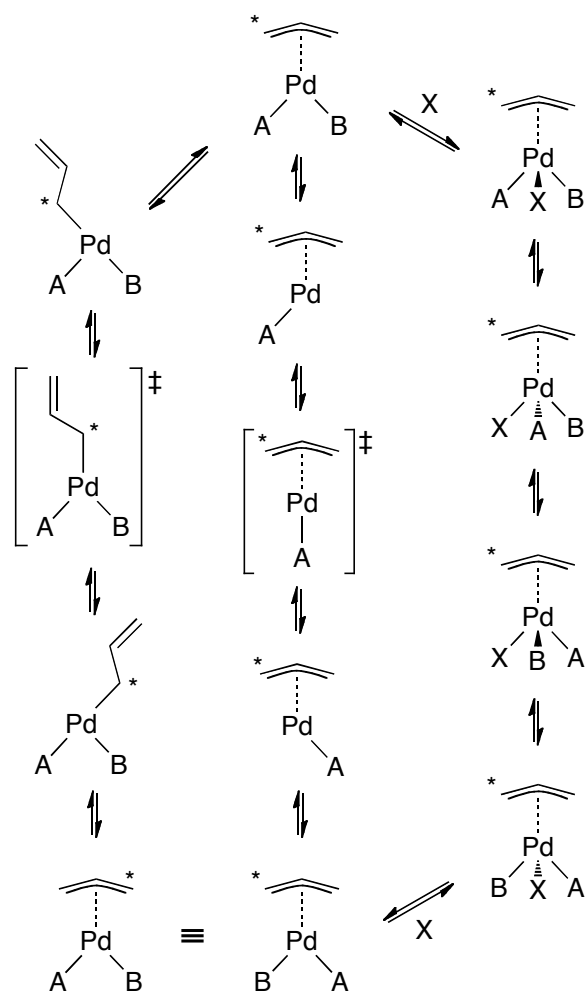


Scheme 2 Two dynamic manifolds of (η^3 -allyl)Pd isomerization.

When the intermediate is an unsymmetrically 1,3-disubstituted allyl, the dynamics occur in two mirror image manifolds that can cross-over, 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. Interestingly, pairs of substrates related by 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 a 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 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, 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 $(\eta^3\text{-allyl})\text{Pd}$ complexes: left hand side, η^3 - η^1 -isomerisation; centre, 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 $(\eta^3\text{-allyl})\text{Pd}$ 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 through hydrogen bonding^{21,22} or by employing an electronically dissymmetric ligand with a strong trans effect difference, like the highly effective PN-ligands.^{23,24,25,26} In the latter case, it is expected that during generation of the η^3 -allyl intermediate from the η^2 -alkenyl precursor, the strongly trans-influence of the phosphorous will result in 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 regioselectivity 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, regioselectivity 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, P,N systems give fast and selective reactions, and thus do not seem to suffer from memory effects. In stark contrast, we have earlier shown^{11,27} that P,Cl systems afford as much as 40% regioselectivity[§] despite there being a much smaller difference in 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, Ph₂P-CH₂CH₂-NMe₂ (**5**) which can be viewed as a chimeric combination of two frequently employed non-chiral palladium ligands, dppe and TMEDA.

Results and discussion

The above 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 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 (Figure 1). As expected, attack trans to phosphorus is favored, by ca 7 kJ/mol. At room temperature, this energy difference corresponds to about an order of magnitude in reactivity difference.

[§] We use 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).

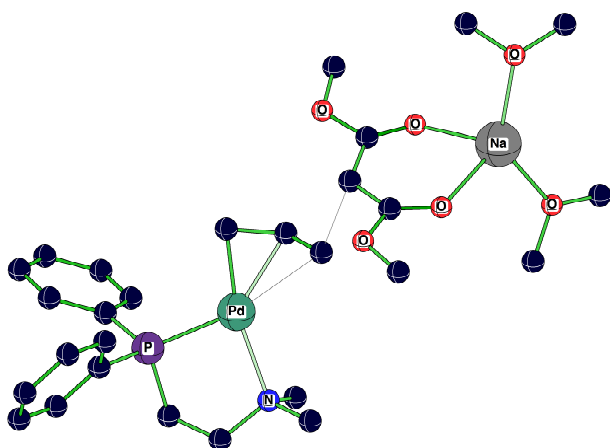
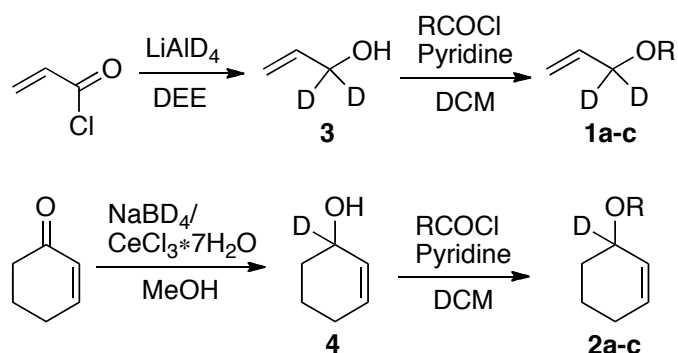


Figure 1 Preferred nucleophilic attack at a (η^3 -allyl)Pd complex with a PN-ligand.

Experimental studies were then carried out with labeled acyclic allylic substrates (**1a-c**), synthesized from acryloyl chloride, and the 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 $\text{Pd}_2(\text{dba})_3$, to give a 1:1 ligand: Pd^0 precatalyst; the reactions were run at room temperature for 20 h under nitrogen atmosphere, (Chart 1). Sodium diethyl methylmalonate was used as nucleophile. No significant regioretention was observed for any of the substrates (entries 1-6, Table 1).

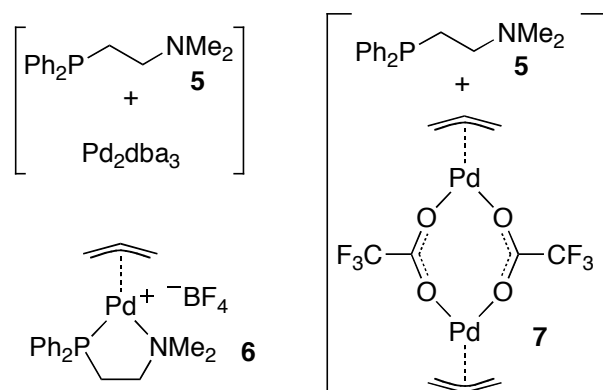


Chart 1 Pre-catalyst complexes

Table 1 Results from the allylic alkylation of **1a-c** and **2a-c** by NaC(Me)(CO₂Et)₂ using Pd complexes of ligand **5**

Entry	Substrate	Pre-catalyst	Retention (%) [§]
1	1a	5 + Pd ₂ dba ₃	-2 ^a
2	1b	5 + Pd ₂ dba ₃	0 ^a
3	1c	5 + Pd ₂ dba ₃	-2 ^a
4	2a	5 + Pd ₂ dba ₃	2
5	2b	5 + Pd ₂ dba ₃	0
6	2c	5 + Pd ₂ dba 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

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

Amatore and Jutand have shown that dba (*E*-dibenzylidene acetone) undergoes equilibrium complexation with [Pd⁰(PPh₃)₂] to generate [Pd⁰(dba)(PPh₃)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, [(η³-allyl)Pd(**5**)]BF₄ (**6**) and [(η³-allyl)PdOCOCF₃]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 regioretention for all of the substrates, entries 7-15 in Table 1, confirming that dba is not an innocent spectator ligand, however the magnitude of the effect is small.

The partial regioretention in the reaction when using **6** or **7** as precatalysts 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 the nucleophilic attack of the malonate on the allyl.

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 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 regioretention would be detected irrespective of whether the alkylation reaction was proceeding with regioretention. 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 addition of the nucleophile (Table 2). After 65 hours, the mixture was quenched and analyzed by ^1H 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 $\text{Pd}_2(\text{dba})_3$ as palladium source (entries 1-6, table 1), but no equilibration of any of the allyls was observed when using pre-catalysts **6** or **7** (entries 7-9 and 13-15, table 2). This suggested that Pd(0) was responsible for 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** (entries 10-12, Table 1) and only a minor extent (5-10%) of equilibration of all the allyls was observed when using **7** (entries 16-18, Table 1), in other words, there is not sufficient equilibration to explain the low regioretention in the reaction. In 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 regioselectivity in the reaction when using **7** as pre-catalyst.

Table 2 *Results from the isomerization experiments*

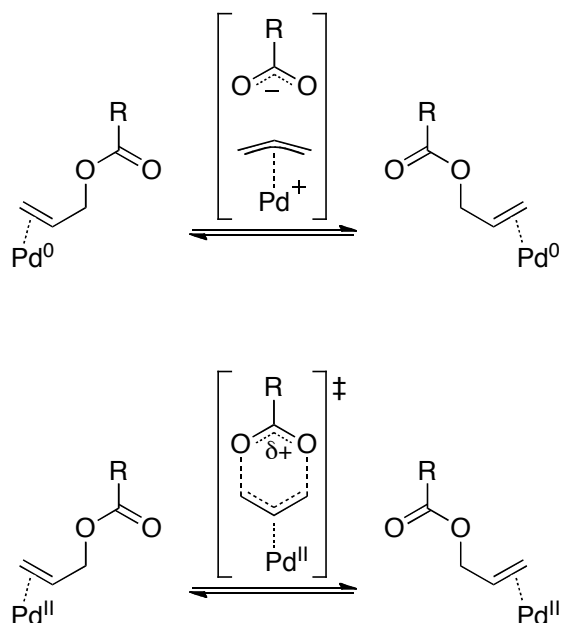
Entry	Substrate	Catalyst	Isomerized allyl
1	1a	5 + Pd ₂ dba ₃	Yes
2	1b	5 + Pd ₂ dba ₃	Yes
3	1c	5 + Pd ₂ dba ₃	Yes
4	2a	5 + Pd ₂ dba ₃	No
5	2b	5 + Pd ₂ dba ₃	Yes
6	2c	5 + Pd ₂ dba ₃	Yes
7	2a	6	No
8	2b	6	No
9	2c	6	No
10	2a	6 + 0.05 eq Nu ⁻	No
11	2b	6 + 0.05 eq Nu ⁻	No
12	2c	6 + 0.05 eq Nu ⁻	No
13	2a	5 + 7	No
14	2b	5 + 7	No
15	2c	5 + 7	No
16	2a	5 + 7 + 0.1eq Nu ⁻	“slight”
17	2b	5 + 7 + 0.1eq Nu ⁻	“slight”
18	2c	5 + 7 + 0.1eq Nu ⁻	“slight”

Isomerization mechanism

We became interested in the mechanism for the equilibration of **2b** and **2c** with their regio-isotopomers. The isomerization of allyls have been the object for several investigations, but mainly concerning the stereochemical aspects of the process.^{30,31,32}

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 Pd₂(dba)₃ added. A detailed analysis of the reaction mixture by GC-MS showed that neither crossover product (cyclohexenyl benzoate and allyl carbonate) were detectable in the reaction mixture after 1h or indeed after 70h 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 rearrangement³³ (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).

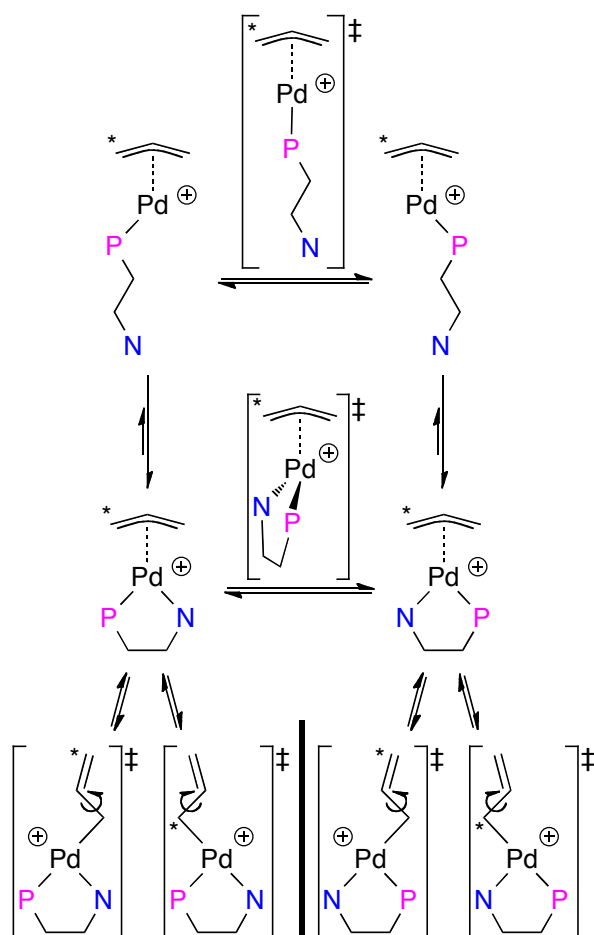


Scheme 5 Plausible Pd(0)- and Pd(II)-assisted pathways for isomerization of allyl substrates

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 PN-ligand, outlined in Scheme 6.

The outcome from our study was surprising. 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 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

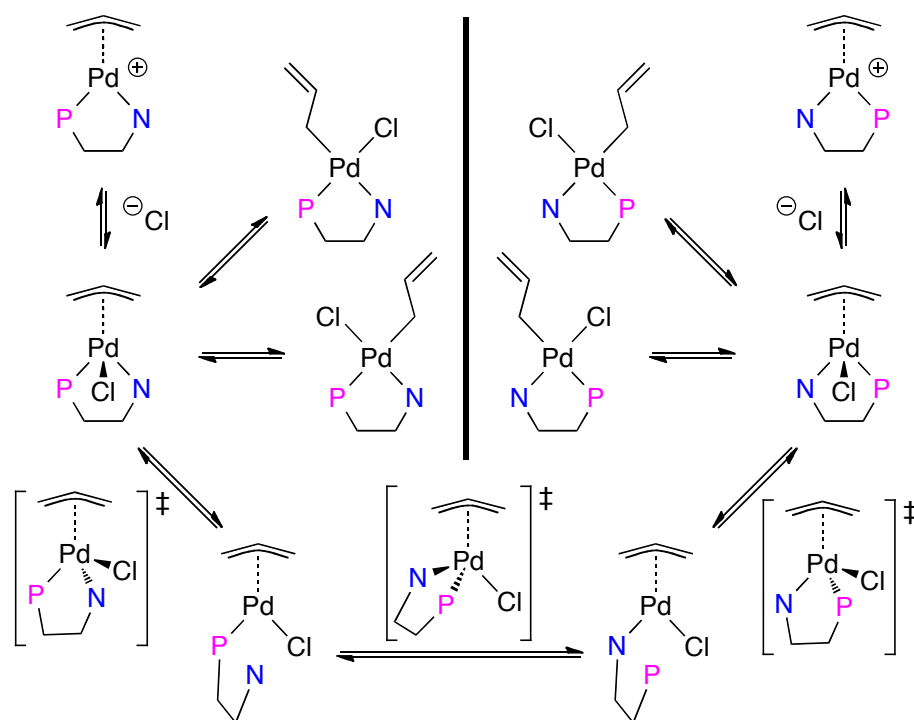
fact the lowest energy path for apparent rotation in the cationic complex, with a free energy barrier of 113 kJ/mol.



Scheme 6 Plausible dynamic processes in $(\eta^3\text{-allyl})\text{Pd}$ complexes with PN-ligands.

We also investigated the effect of added anionic ligands, modeled by chloride anion (Scheme 7). Here too there were some surprises. There are no ground state structures corresponding to trigonal bipyramids. All 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 able to accept electron pairs from outside the coordination plane. An X-ray structure of a presumed pentacoordinate $(\eta^3\text{-allyl})\text{Pd}$ complex with phenanthroline and chloride²⁰ does in fact correspond 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. Interestingly, 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 advanced by Landis and Weinhold.³⁴



Scheme 7 Chloride-assisted dynamic processes in $(\eta^3\text{-allyl})\text{Pd}$ complexes with PN-ligands.

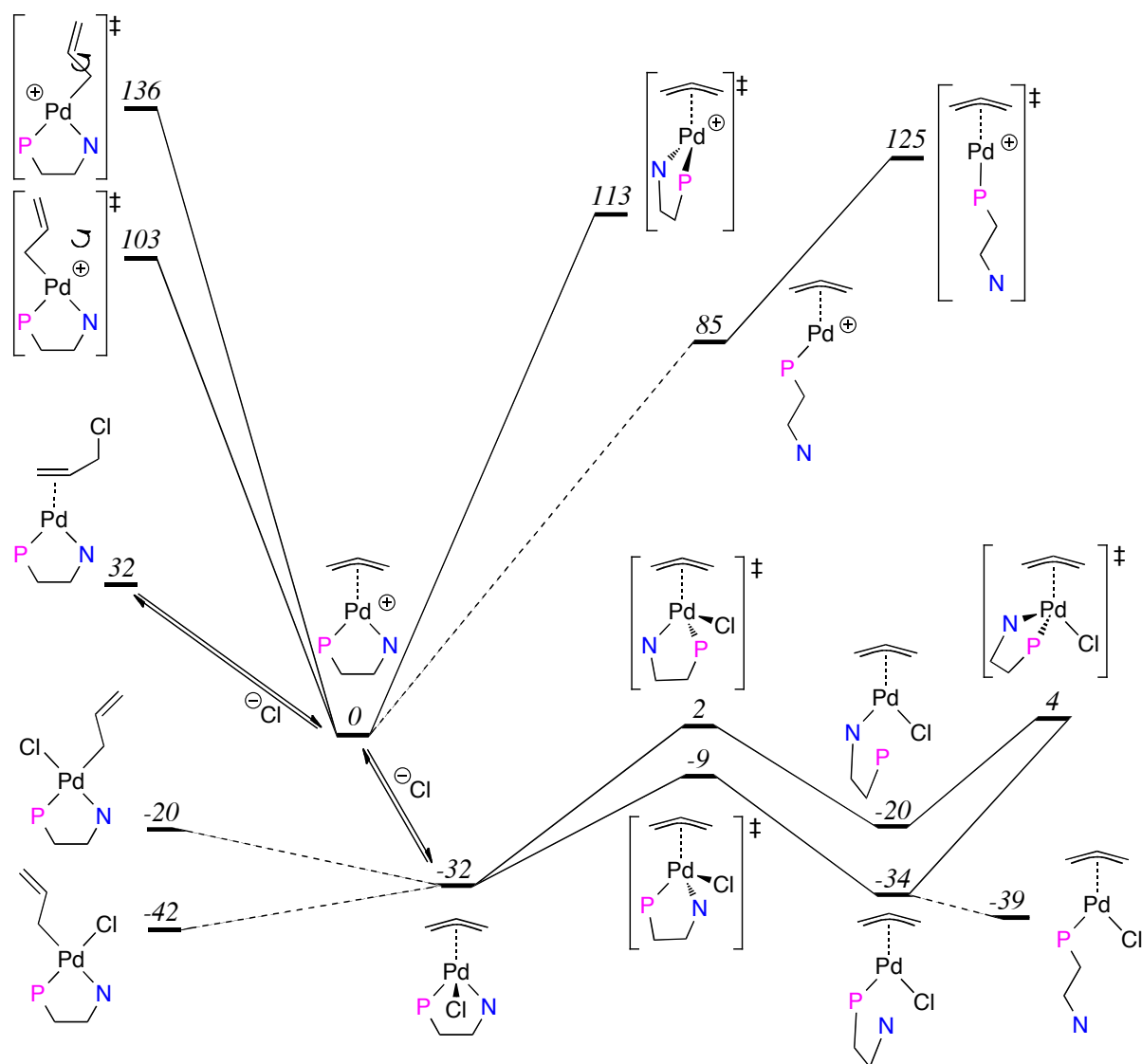
The $(\eta^1\text{-allyl})\text{Pd}$ complexes are stable, square planar structures when coordinated with a chloride ligand (Scheme 7). This is in agreement with the observation that syn-anti isomerization is strongly accelerated by chloride, but also shows that this process cannot be responsible for 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 at 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 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, in agreement with 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 like chloride. Even the small amount of comparatively weak acetate ligand present in the catalytic reactions will be able to catalyze the apparent rotation, 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 Pd⁰/allyl chloride complex at 32 kJ/mol deserves some comment. 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 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 Pd⁰/allyl carboxylate complex could become significant, or even the resting state.³⁵



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

Conclusions

The expected regioselectivity in allylic alkylations with deliberately simple P,N-ligand 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, like the leaving group, suppresses the memory effect. This is a strong indication that apparent rotation is fast compared to nucleophilic attack for the intermediate $(\eta^3\text{-allyl})\text{Pd}$ complex, and that the apparent rotation is catalyzed by anionic ligands in solution, in good agreement with 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 counterions. 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)Pd⁰ 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, maybe even disappearing.³⁵

Reversibility of the initial ionization could also help rationalize the starting material racemization observed here. However, as evidenced by lack of leaving group exchange in cross-over 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).

Experimental

General

All reactions were performed in oven-dried glassware and under nitrogen atmosphere, except the synthesis of cyclohexenol. Solvents were distilled prior to use. THF was distilled from Na/benzophenone, CH₂Cl₂ and pyridine from CaH₂, under a nitrogen atmosphere. DEE was purchased as anhydrous and stored over molecular sieves (4Å). Commercially available reagents were used as delivered unless stated otherwise. TLC was performed using alumina

plates coated with silica gel 60, F₂₅₄. The plates were visualized by using a mixture of 2% KMnO₄ and 4% K₂CO₃ (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 ¹³C 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 CDCl₃ and chemical shifts are given in ppm relative to residual CHCl₃ (7.27 ppm).

Substrates were synthesized using modified literature procedures.

Allyl alcohol-1-D₂ 3³⁷

LiAlD₄ (262 mg, 6.25 mmol) was added to dry DEE (15 ml) at 0°C. The solution was flushed with N₂ and then cooled to 0°C in an ice-bath. Acryloyl chloride (813 μl, 10 mmol) was added drop wise. The reaction mixture was stirred at 0 °C for 2 hours. The reaction was thereafter quenched with H₂O (260 μl), NaOH (15%, 260 μl), and H₂O (790 μl), then stirred at room temperature for 30 min. The white precipitate was filtered off and washed with DEE (2-3 ml). The solution was dried with MgSO₄, 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, CDCl₃): δ (ppm) 5.99 (m , 1H), 5.27 (m, 1H), 5.14 (m ,1H).

Cyclohexenol-1-D 4³⁸

Cyclohexenone (2.42 ml, 25 mmol) was added to a solution of CeCl₃*7H₂O (9.3g, 25 mmol) in methanol (20 ml). After cooling to 0 °C, NaBD₄ 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 (1M, 30 ml), and the product was extracted with DEE (3×20 ml), washed with brine (15 ml), then dried over MgSO₄ and yielded the pure product after evaporation of the solvent, as a clear oil (2.2 g, 90%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.84 (m, 1H), 5.75 (m, 1H), 1.54-2.19 (m, 6H).

Synthesis of allylic acetates ¹¹

1a

Acetyl chloride (570 μ l, 8.0 mmol) and pyridine (645 μ l, dry, 8.0 mmol) were added in portions to a cooled solution of **3** (0.36 g, 6 mmol) in DCM (15 ml, dry) at 0 °C. A white precipitate formed almost immediately. The reaction mixture was allowed to reach room temperature during 20 h. Reaction mixture was cooled again and the formed precipitate was filtered off and washed with DCM. The solution was washed with ice-water (10 ml), ice-cooled brine (15 ml), dried with Na₂SO₄ 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, CDCl₃): 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).

2a

Acetyl chloride (1.10 ml, 15 mmol) and pyridine (1.20 ml, dry, 15 ml) were added in portions to a cooled solution of **4** (0.99 g, 10 mmol) in dry DCM (15 ml), at 0 °C. A white precipitate formed almost immediately. The reaction mixture was allowed to reach room temperature during 20 h, and was then quenched with NH₄Cl (aq. sat., 20 ml). The product was extracted with DCM (2 \times 25 ml), washed with aq. saturated NaHCO₃ (25 ml), brine (25 ml), and then dried with MgSO₄, 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 (0.85g, 6.0 mmol, 60%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.95 (m, 1H), 5.68 (m, 1H), 5.24 (m, 1H) absent when D, 1.55-2.10 (m, 9H).

General procedure for the synthesis of allylic benzoates

Pyridine (970 μ l, 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 DCM (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 H₂O (20

ml) and brine (20 ml), then dried with MgSO₄. 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).

¹H NMR (400 MHz, CDCl₃): **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).

General procedure for the synthesis of allylic carbonates³⁹

Pyridine (806 μl, 10 mmol) was added to a cooled solution of cyclohexenol (0.78 g, 8 mmol) in DCM (15 ml). Thereafter methyl chloroformate (770 μl, 10 mmol) was added dropwise, and a white precipitate started forming. The stirred solution was allowed to reach room temperature during 17 hours. H₂O (15 ml) was added and the product was extracted with DCM (3×20 ml). The organic phase was washed with 1M HCl (2×20 ml), H₂O (15 ml), and brine (15 ml). Thereafter dried with MgSO₄, 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%).

¹H NMR (400 MHz, CDCl₃): **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).

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 N₂. Diphenylphosphine (1.73 ml, 10 mmol) was added and the orange-red solution was stirred at room temperature for 30 minutes. 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 DEE (25 ml), and then made alkaline with 5M

NaOH. The product was extracted with DEE (3×25 ml), the organic phase was washed with brine (20 ml), dried with Na₂SO₄ and the crude product was obtained as a cloudy oil after evaporation. The oil was dissolved in a small amount of DEE and filtered through a column of basic alumina, yielding the product as a clear oil (0.73 g, 2.8 mmol, 28%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.40-7.48 (m, 4H), 7.29-7.38 (m, 6H), 2.36-2.46 (m, 2H), 2.21-2.28 (m, 8H).

[(η³-allyl)Pd(5**)]BF₄ **6**³**

[(η³-allyl)PdCl]₂ (18.3 mg, 0.05 mmol) in DCM (1 ml) was added to AgBF₄ (20.4 mg, 0.105 mmol), under N₂. A white precipitate was formed almost immediately. The solution was stirred at 20 °C for 15 minutes. **5** (25.7 mg, 0.10 mmol) was added, whereupon the solution turned brown and was stirred for 1h. 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%).

¹H NMR (400 MHz, CDCl₃): 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).

[(η³-allyl)PdOCOCF₃]₂ **7⁴¹**

Pd(dba)₂ (57.5 mg, 0.10 mmol) was dissolved in dry THF (0.8 ml) and carefully evacuated, then re-filled with N₂ 3 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 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 H₂O (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%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.61 (m, 1H), 4.14 (m, 2H), 3.07 (m, 2H).

General procedure for the allylic alkylation ¹¹

NaH (40 mg, 1 mmol, 60% suspension in oil), was dissolved in dry THF (2 ml), the flask was evacuated and refilled with N₂. Diethyl methylmalonate (170 μ l, 1 mmol) was added drop wise to the suspension, which turned clear after the addition. The solution was stirred at room temperature for 10 minutes.

Either Pd₂(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 N₂ three times. **5** (6.2 μ l, 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.

Or **6** (0.01 mmol, 5 mg) in DCM (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 hours. Reaction mixture was diluted with DEE (5 ml), and washed with 1M HCl (5 ml), H₂O (5 ml), and brine (5 ml). Thereafter it was dried with Na₂SO₄ and the product mixture was obtained as a yellow oil, after evaporation of solvents. The crude mixture was analyzed without further purifications.

¹H NMR (400 MHz, CDCl₃): **8** δ (ppm) 5.69 (m, 1H), 5.10 (m, 2H), 4.19 (q, 4 H), 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).

Computational Details

All DFT calculations were performed in the Jaguar program^s using the B3LYP functional^{42,43,44} 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

^s Jaguar v. 7.6 from Schrödinger, Inc., see: <http://www.schrodinger.com>

gas phase. No standard state corrections have been applied; energies are appropriate for 1M 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've 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 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 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 H₂P-CH₂CH₂-NH₂ 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 entropic contributions and thus to favor 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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