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Memory Effects in Palladium-Catalyzed Allylic Alkylations of 2-Cyclohexen-1-yl Acetate

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This paper is dedicated to Professor J.-E. Bäckvall on the occasion on his 60th birthday.

Abstract: The objective of this work was to characterize the enantiospecificity of the allylic alkylation of enantioenriched 2-cyclohexen-1-yl acetate with the enolate ion of dimethyl malonate catalyzed by unsymmetrical palladium catalysts. The precatalysts employed were (η^3-allyl)PdLCl, where L is a monophosphine ligand [PPh_3, PCy_3, P(2-BiPh)Cy_2, or P(*t*-Bu)$_3$], all of which afforded enantiospecificity to some extent (5–47%). Quantum mechanical calculations show that, theoretically, the enantiospecificity should be high due to a preference for the "*trans* to P" transition state in both formation of the η^3-allyl intermediate and nucleophilic attack. However, the observed enantiospecificity is relatively low due to isomerization of the η^3-allyl intermediate and/or dynamic equilibria between the catalytically active (η^3-allyl)PdLCl species and $[(\eta^3\text{-allyl})PdL_2]^+$ or $[(\eta^3\text{-allyl})PdCl]_2$. It was also observed experimentally that increasing the bulk of the phosphine inhibits formation of the $[(\eta^3\text{-allyl})PdL_2]^+$ complexes, significantly increasing the observed enantiospecificity for some of the ligands.

Keywords: allylic substitution; chloride effect; enantiospecificity; memory effect; palladium; regiospecificity

Introduction

The formation of C–C bonds with transfer of chirality is of great importance in modern organic synthesis. One of the most versatile methods is the Pd-catalyzed allylic substitution reaction (the Tsuji–Trost reaction, see Figure 1),[1–3] which normally proceeds under much milder conditions than regular S_N2 reactions and often gives rise to high chemo-, regio-, and stereospecificity (or selectivity). Leaving groups are often acetates or carbonates instead of the more reactive halides and sulfonates, which can be advantageous in multistep syntheses. The Tsuji–Trost reaction has been extensively studied and the mechanism has been investigated in detail.[2,3] However, in some cases a *memory effect* complicates the pattern of reactivity and this effect is not well understood,[4–6] although efforts have been made to study the mechanistic traits of memory effects.[7] The work presented here is an extension of an earlier study of the Tsuji–Trost reaction of a series of isomeric butenyl substrates,[5] and in the present investigation we have focused on enantiospecificity in the allylic alkylation of enantioenriched 2-cyclohexen-1-yl acetate.

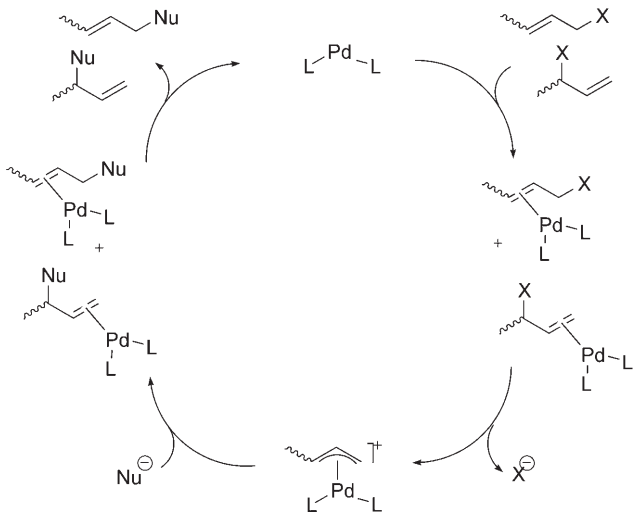

Figure 1. Proposed mechanism for Tsuji–Trost reaction.[2] L denotes a neutral ligand.

The Tsuji–Trost reaction may result in either retention of the olefin at its original position or allylic rearrangement[2,3] (Figure 1). The initially proposed mechanism involves complexation between the olefin and Pd(0) followed by displacement of the allylic leaving group. This leads to the formation of an (η^3-allyl)-Pd(II) intermediate, which is attacked by a soft nucleophile at either terminus of the allyl moiety. Hereby Pd(0) is released and the catalytic cycle completed (Figure 1).

From the above scheme it can be predicted that isomeric allylic substrates should yield the same distribution of products. In particular, when the allylic acetate is chiral but yields a C_s-symmetric (η^3-allyl)Pd intermediate, as in the most common test cases for asymmetric versions of the reaction, the inherent preference for the two enantiomers of the product should, in the absence of chiral ligands, be equal. However, isomeric allylic substrates do not always yield the same distribution of products, due to regiospecificity in the reaction (Figure 2).

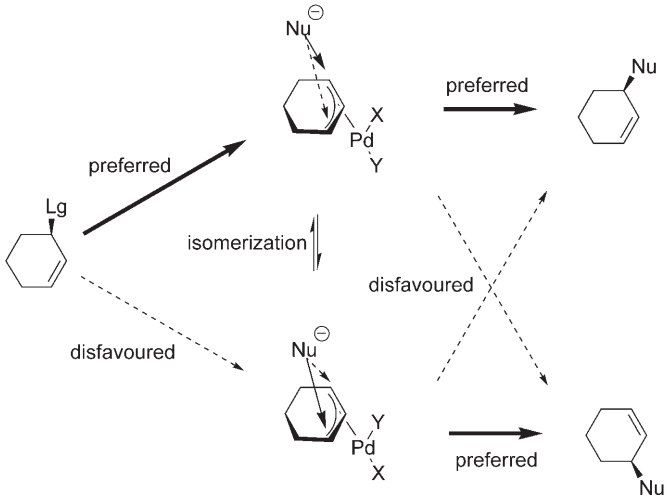

Figure 2. Proposed mechanism for the asymmetric version of the Tsuji–Trost reaction of cyclohexenyl systems. Lg: leaving group. Nu: nucleophile. X, Y: different ligands.

In some cases, partial retention of the enantiomeric purity has been observed in Pd-catalyzed allylic alkylations of acetates.[4–6] This phenomenon, which conflicts with the proposed reaction mechanism, has been dubbed the "memory effect",[2,3,5,6] and this may refer to both stereo- and regiospecificity.

We reasoned that in order to characterize such memory effects the Tsuji–Trost reaction of a monosubstituted cyclic substrate with a soft nucleophile would be advantageous, as this leads to an intermediate that is symmetric with respect to the allyl with only two possible reaction sites (Figure 2). Consequently, any observed specificity is caused by transfer of stereoinformation from the starting material to the product *via* the dissymmetry of the η^3-allyl intermediate. The product distribution and thereby the characterization of the specificity is thus simplified since only enantiomers and not other stereoisomers of the product are formed. We therefore chose to work with enantioenriched 2-cyclohexen-1-yl acetate as the substrate.

There is clear evidence that the η^3-allyl intermediate in the Tsuji–Trost reaction of cyclic substrates is formed by attack of Pd(0) on the face of the allylic system opposite to the leaving group.[4,8,9] However, during the attack of Pd(0) the leaving group may be positioned either *trans* or *cis* to the ligand X, and the subsequent nucleophilic attack on the η^3-allyl intermediate may also occur either *trans* or *cis* to X. Thus, for enantioenriched substrates, enantiospecificity (a memory effect) will be possible only if the η^3-allyl intermediate is unsymmetric and if the catalyst shows some regiochemical preference in both formation and reaction of the intermediate (Figure 2). In addition, the magnitude of any observed enantiospecificity will be dependent on factors such as competition of the external nucleophilic attack with the unimolecular isomerization of the η^3-allyl intermediate and other equilibria involving the intermediate, for example external attack by Pd(0).[10–12]

The preference of one reaction site in the η^3-allyl species over the other is due to a difference between the two remaining ligands, X and Y, on palladium (Figure 2), which may be sterically or electronically different. Since previous results from allylic alkylations of acyclic substrates catalyzed by the unsymmetrical (η^3-allyl)PdPPh_3Cl precatalyst had afforded specificity,[5] it was assumed that this precatalyst would also afford enantiospecificity in the reaction of enantioenriched 2-cyclohexen-1-yl acetate (Figure 3).

Results

A reaction catalyzed by the symmetrical [(η^3-allyl)Pd-$(PPh_3)_2$]$^+$ precatalyst led, as expected, to a racemic product, whereas use of the (η^3-allyl)PdPPh_3Cl precatalyst gave some enantiospecificity (Table 1, entries 1 and 2). These experiments also verified that [(η^3-allyl)Pd$(PPh_3)_2$]$^+$ reacted much faster than (η^3-allyl)PdPPh_3Cl.[13] It has been shown that [(η^3-allyl)Pd-$(PPh_3)_2$]$^+$ and (η^3-allyl)PdPPh_3Cl are in equilibrium with each other,[11–13] which should lead to an erosion of enantiospecificity even if preformed (η^3-allyl)PdPPh_3Cl is employed as precatalyst. Furthermore, an excess of PPh_3 relative to Pd would be devastating to the enantiospecificity because of formation of [(η^3-allyl)Pd$(PPh_3)_2$]$^+$ as the major catalytically active species.

The influence of the phosphine ligand was then investigated (Table 1, entries 3–5), and the presence of

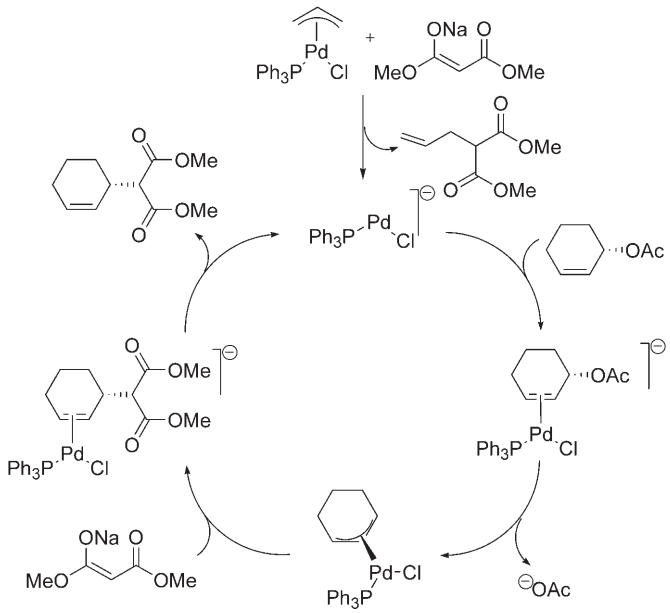

Figure 3. Proposed preferred reaction pathway for the Tsuji–Trost reaction of (*S*)-2-cyclohexen-1-yl acetate, the unsymmetrical (η^3-allyl)PdPPh$_3$Cl precatalyst, and the enolate ion of dimethyl malonate as nucleophile.

cyclohexyl moieties on the phosphine was found to be favourable (*cf.* Table 1, entries 2 and 3) while the very bulky alkylphosphine P(*t*-Bu)$_3$ was detrimental to both enantiospecificity and reaction rate (Table 1, entry 5). The increase in enantiospecificity when going from the aromatic phosphine, PPh$_3$, to the alkyl phosphine, PCy$_3$, can probably not be explained by steric effects alone and there is an electronic difference in that Cy is more electron-donating than Ph. We have compared these catalyst systems computationally and a discussion is given later.

The increased bulk of the phosphine in the (η^3-allyl)PdPCy$_2$(2-BiPh)Cl precatalyst could hinder rotation of the η^3-allyl moiety leading to an increase in the enantiospecificity. However, if the steric bulk is exceedingly high [i.e., with (η^3-allyl)PdP(*t*-Bu)$_3$Cl] a large decrease in the reaction rate is observed. In this case enantiospecificity is also lowered probably due to competition between the nucleophilic attack and the isomerization of the η^3-allyl intermediate (Table 1, entries 4 and 5).

It has been shown that the chloride anion has a significant effect on the outcome of the Tsuji–Trost reaction,[5] and therefore it was of interest to study the effects of Cl$^-$ on the enantiospecificity in the present case. Since the (η^3-allyl)PdP(2-BiPh)Cy$_2$Cl and (η^3-allyl)PdPCy$_3$Cl precatalysts showed the highest enantiospecificity in the previous experiments (see Table 1) these were chosen for a series of reactions starting with [(η^3-allyl)PdCl]$_2$ and adding increasing amounts of (2-BiPh)PCy$_2$ or PCy$_3$ (Figure 4 Table 2). We assume that at phosphine concentrations lower than 2 equivs. per Pd, chloride is still bound to Pd.

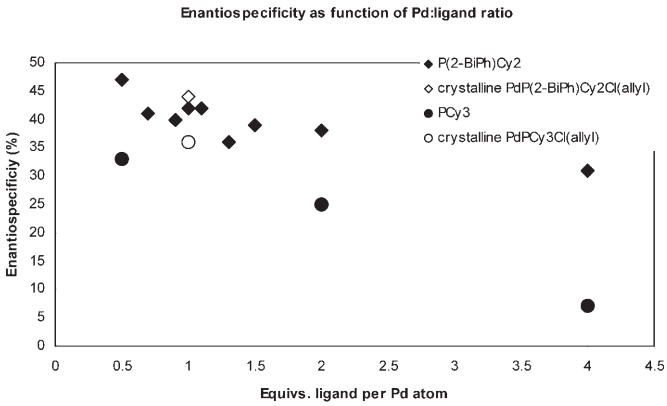

Figure 4. The square data points are reactions performed with addition of P(2-BiPh)Cy$_2$, whereas round data points represent addition of PCy$_3$. Hollow data points are obtained using the crystalline η^3-allyl complexes as catalysts.

The enantiospecificity in these experiments shows certain trends, maximum enantiospecificity being obtained when the phosphorus ligand:Pd ratio is unity or smaller (Table 2, entries 1 and 12). Hereafter the enantiospecificity decreases slowly with increase in P(2-BiPh)Cy$_2$ concentration and decreases more rapidly with increase in PCy$_3$ concentration. It should be noted that Pd black precipitates after a while at low phosphorus ligand concentrations. However, monitoring of the reactions by GC shows that the enantiospe-

Table 1. Allylic alkylations of 2-cyclohexen-1-yl acetate with dimethyl malonate and NaHMDS.

Entry	Pd complex	Acetate *ee*[a]	Product *ee*[a]	Enantiospecificity[b]	Reaction after 16 h[a]
1	[(η^3-allyl)PdCl]$_2$ + 2 equivs. PPh$_3$	95 %	racemate	-	100 %
2	(η^3-allyl)PdPPh$_3$Cl	95 %	15 %	16 %	40 %
3	(η^3-allyl)PdPCy$_3$Cl	90 %	32 %	36 %	5 %
4	(η^3-allyl)PdP(2-BiPh)Cy$_2$Cl	90 %	40 %	44 %	15 %
5	(η^3-allyl)PdP(*t*-Bu)$_3$Cl	90 %	6 %	7 %	1.5 %

[a] Determined by chiral GC.
[b] Calculated as *ee* of product divided by *ee* of starting material.

Table 2. Dependence of enantiospecificity on equivalents phosphorus ligand per Pd atom in allylic alkylations of 90% *ee* 2-cyclohexen-1-yl acetate.

Entry	Pd complex	Ligand added	Product *ee*[a]	Enantiospecificity[b]
1	$[(\eta^3\text{-allyl})PdCl]_2$	0.5 equivs. P(2-BiPh)Cy_2	42%	47%
2	$[(\eta^3\text{-allyl})PdCl]_2$	0.7 equivs. P(2-BiPh)Cy_2	37%	41%
3	$[(\eta^3\text{-allyl})PdCl]_2$	0.9 equivs. P(2-BiPh)Cy_2	36%	40%
4	$[(\eta^3\text{-allyl})PdCl]_2$	1.0 equiv P(2-BiPh)Cy_2	38%	42%
5	$[(\eta^3\text{-allyl})PdCl]_2$	1.1 equivs. P(2-BiPh)Cy_2	38%	42%
6	$[(\eta^3\text{-allyl})PdCl]_2$	1.3 equivs. P(2-BiPh)Cy_2	33%	36%
7	$[(\eta^3\text{-allyl})PdCl]_2$	1.5 equivs. P(2-BiPh)Cy_2	34%	39%
8	$[(\eta^3\text{-allyl})PdCl]_2$	2.0 equivs. P(2-BiPh)Cy_2	34%	38%
9	$[(\eta^3\text{-allyl})PdCl]_2$	4.0 equivs. P(2-BiPh)Cy_2	28%	31%
10	$[(\eta^3\text{-allyl})PdCl]_2 + AgBF_4$	4.0 equivs. P(2-BiPh)Cy_2	Pd(0) precipitates	-
11	$(\eta^3\text{-allyl})PdP(2\text{-BiPh})Cy_2Cl$	-	40%	44%
12	$[(\eta^3\text{-allyl})PdCl]_2$	0.5 equivs. PCy_3	30%	33%
13	$[(\eta^3\text{-allyl})PdCl]_2$	2.0 equivs. PCy_3	22%	25%
14	$[(\eta^3\text{-allyl})PdCl]_2$	4.0 equivs. PCy_3	6%	7%
15	$(\eta^3\text{-allyl})PdPCy_3Cl$	-	32%	36%

[a] Determined by GC.
[b] Calculated as *ee* of product divided by *ee* of starting material.

cificities are unchanged during the reaction even when Pd black precipitates (results not shown).

The symmetrical $[(\eta^3\text{-allyl})Pd(P(2\text{-BiPh})Cy_2)_2]^+$ and $[(\eta^3\text{-allyl})Pd(PCy_3)_2]^+$ complexes are assumed to afford a racemate regardless of the *ee* of the starting material. To further investigate this assumption, formation of $[(\eta^3\text{-allyl})Pd(P(2\text{-BiPh})Cy_2)_2]^+$ was attempted by adding 4 equivalents P(2-BiPh)Cy_2 per Pd atom to $[(\eta^3\text{-allyl})PdCl]_2$ and removing Cl^- with $AgBF_4$. However, this caused Pd black to precipitate, which shows that Cl^- is needed to stabilize the catalyst and that probably the $[(\eta^3\text{-allyl})Pd(P(2\text{-BiPh})Cy_2)_2]^+$ complex hardly forms, due to the bulk of the P(2-BiPh)Cy_2 ligand. Thus, it is concluded that $[PdP(2\text{-BiPh})Cy_2Cl]^-$ is the catalytically active species. These results correlate well with previous findings, where chloride anions have a positive effect on enantiospecificity in Pd-catalyzed allylic alkylations.[4–6]

For both precatalysts the enantiospecificity obtained using the preformed complexes was of the same order of magnitude as when the precatalysts were formed *in situ* (Table 2, *cf.* entries 1 and 11, and entries 12 and 15). This is in agreement with our initial assumption that Cl^- stays bound to Pd during addition of phosphine.

As the preceding allylic alkylations of 2-cyclohenen-1-yl acetate of 90% *ee* with the enolate ion of dimethyl malonate were very slow at ambient temperature, the reaction mixtures were heated to 40 °C (Table 3). However, this caused Pd black to precipitate after ~30 min and not surprisingly a decrease in the enantiospecificity was observed.

In another attempt to increase the reaction rate and perhaps also the enantiospecificity, the allylic alkylations of 2-cyclohexen-1-yl acetate were carried out in the presence of the Na-chelating agent 15-crown-5. Madec et al. have shown that the rate of allylic alkylations catalyzed by $(\eta^3\text{-allyl})Pd(PPh_3)_2$ is drastically increased in the presence of 15-crown-5.[14] Thus, reactions with the four $(\eta^3\text{-allyl})PdLCl$ precatalysts, where L is PPh_3, PCy_3, P(2-BiPh)Cy_2, or P(*t*-Bu)$_3$, were carried out in the presence 15-crown-5 (Table 4).

Disappointingly, in contrast to the results of Madec et al., the reaction rates were not increased by addition of 15-crown-5 (results not shown) and the enantiospecificity was decreased compared to the reactions without 15-crown-5. The observed decrease in enantiospecificity upon removal of Na^+ ions could indicate that the ion-pairing mechanism suggested by Trost

Table 3. Allylic alkylation of 90% *ee* 2-cyclohexen-1-yl acetate with dimethyl malonate and NaHMDS at 22 °C and 40 °C.

Entry	Pd complex	Reaction temperature	Acetate *ee*[a]	Product *ee*[a]	Enantiospecificity[b]
1	$(\eta^3\text{-allyl})PdP(2\text{-BiPh})Cy_2Cl$	22 °C	90%	40%	44%
2	$(\eta^3\text{-allyl})PdP(2\text{-BiPh})Cy_2Cl$	40 °C	90%	25%	28%

[a] Determined by GC.
[b] Calculated as *ee* of product divided by *ee* of starting material.

Table 4. Allylic alkylations of 2-cyclohexen-1-yl acetate with preformed enolate from dimethyl malonate and NaHMDS and 0.2 equivs. 15-crown-5.

Entry	Pd complex	Acetate *ee*[a]	Product *ee*[a]	15-crown-5	Enantiospecificity[b]
1	(η^3-allyl)PdPPh$_3$Cl	90%	racemate	0.2 equivs.	0%
2	(η^3-allyl)PdPPh$_3$Cl	95%	15%	-	16%
3	(η^3-allyl)PdPCy$_3$Cl	90%	16%	0.2 equivs.	18%
4	(η^3-allyl)PdPCy$_3$Cl	90%	32%	-	36%
5	(η^3-allyl)PdP(2-BiPh)Cy$_2$Cl	90%	27%	0.2 equivs.	30%
6	(η^3-allyl)PdP(2-BiPh)Cy$_2$Cl	90%	40%	-	44%
7	(η^3-allyl)PdP(*t*-Bu)$_3$Cl	90%	4%	0.2 equivs.	5%
8	(η^3-allyl)PdP(*t*-Bu)$_3$Cl	90%	6%	-	7%

[a] Determined by GC.
[b] Calculated as *ee* of product divided by *ee* of starting material.

and Bunt is indeed operating under these reaction conditions.[15]

Computational Study

In an attempt to understand the observed memory effect in the experimental study we have undertaken a complementary computational investigation. Earlier we had studied and documented the preference for ionization and nucleophilic attack *trans* to phosphorus when a PMe_3 model phosphine was used.[5,16] Here we wish to extend this study to incorporate the full phosphine ligands used in the experiments, which should allow for a correct description of the combined steric and electronic effects of each ligand. However, in spite of the very rapid development of computer hardware and improved efficiency of the computational code, we still have to impose some limitations to the size of the systems studied. The initial structural evaluation of the (η^3-allyl)PdLCl complexes was performed *in vacuo*. The study of the difference in reactivity between the two allylic termini was performed using an unsubstituted allyl fragment but incorporating an implicit solvation model. The presence of a solvation model in combination with an ammonia probe nucleophile gives a realistic description of the tendency to undergo nucleophilic addition.[17]

Initially, the (η^3-cyclohexenyl)PdLCl complexes were optimized *in vacuo*, which allowed a comparison of the influence of different phosphine ligands on the geometry of the allyl (see Computational Details for further information). With P(2-BiPh)Cy$_2$ as ligand two different energy minima existed, with the biphenyl moiety in either a position proximal to the allyl or in a distal position (Figure 5). In this case a dihedral driver along the appropriate Pd–P–C–C torsion was performed using molecular mechanics, which was then followed by two distinct DFT geometry optimizations. The conformation with the biphenyl moiety proximal to the η^3-(cyclohexenyl) moiety was found

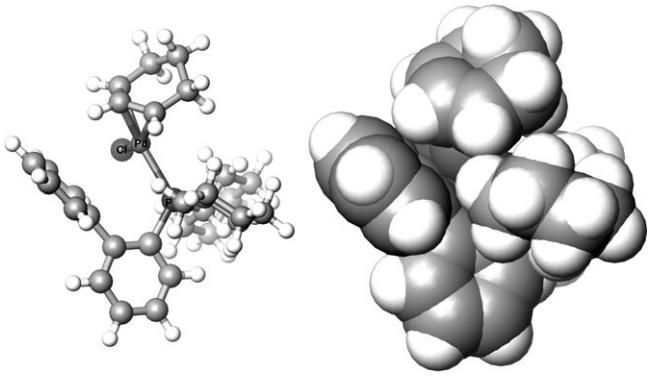

Figure 5. The structure of the lowest energy conformation of the complex with P(2-BiPh)Cy$_2$ as ligand; *left:* ball-stick representation, *right:* space-filling representation at 100% vdW radius.

to be 14 kJ mol^{-1} lower in energy, and from the molecular mechanics-based torsional driver the barrier for rotation was estimated to be about 90 kJ mol^{-1}. The closest ligand-allyl interaction is a 2.97 Å, which is the distance from the central allylic H-atom to one of the carbon atoms in the biphenyl moiety, which fits well with the combined van der Waals radii of C and H.[18] This is a good indication that the biphenyl moiety is stabilized in the position proximal to the allyl where it can interact with the allyl moiety.

The inherent electronic difference between phosphorus and chloride results in a difference in Pd–C bond lengths even in the absence of additional steric interactions,[19] as illustrated with PPh_3 where the two Pd–C bonds are 2.201 Å and 2.253 Å, *trans* to chloride and phosphorus, respectively (Figure 6, *left*). When the phosphine ligand is changed to PCy_3 the increased *trans*-influence of alkylphosphine results in an increased Pd–C bond length (to 2.268 Å) whereas the Pd–C bond length *trans* to chloride remains essentially unchanged (2.202 Å) (Figure 6, *right*).

Since the P(2-BiPh)Cy$_2$ ligand contains one aromatic substituent and two alkyl substituents on phospho-

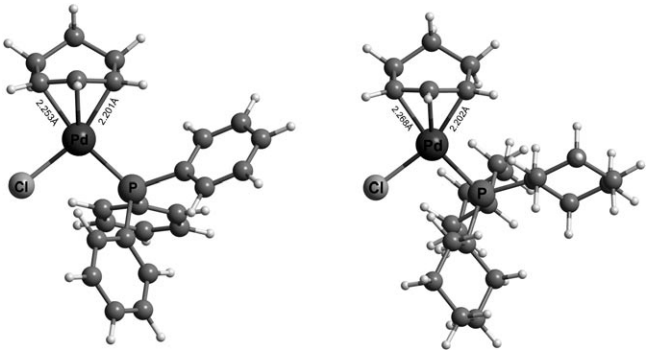

Figure 6. Comparison of the two η^3-(cyclohexyl)allyl bearing either a PPh_3 ligand (*left*) or a PCy_3 ligand (*right*).

rus a *trans*-effect in between those of PPh_3 and PCy_3 can be expected. The resulting structure is in good agreement with this initial expectation and has bond lengths of 2.225 Å and 2.241 Å, respectively, for the Pd–C bonds *trans* to chloride and phosphorus (Figure 7, *left*). Finally, the very sterically encumbered $P(t\text{-}Bu_3)_3$ was investigated which resulted in a structure with the longest Pd–C bond *trans* to the chloride atom (2.258 Å *vs.* 2.233 Å for the bond *trans* to phosphorus). When investigating the structure in more detail it is obvious that the steric interactions between the *tert*-butyl group and the allyl moiety simply force the allyl moiety away from the phosphine ligand, thus effectively overcoming the inherent electronic difference between the two donor atoms. In addition, the steric influence is also manifested in an enlargement of the C–Pd–P angle from 103–105° to 109° (Figure 7, *right*).

One of the most obvious reasons for erosion of the memory effect is the competing reaction of the cationic, diphosphine-ligated allylpalladium complex. To estimate the relative importance of this competing reaction pathway we have energy-minimized both the mixed phosphine-chloride ligated and diphosphine-ligated allylpalladium complexes for each of the four phosphine ligands (Figure 8). To avoid a comparison

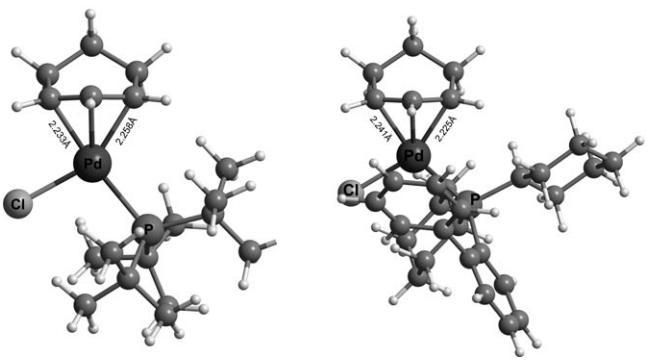

Figure 7. The structure of the η^3-(cyclohexenyl)allyl with the $P(t\text{-}Bu)_3$ ligand (*left*). The large ligand is forced downwards by the steric repulsion from the allyl moiety. The most favourable conformation for the η^3-(cyclohexyl)allyl with the $P(2\text{-BiPh})Cy_2$ ligand (*right*).

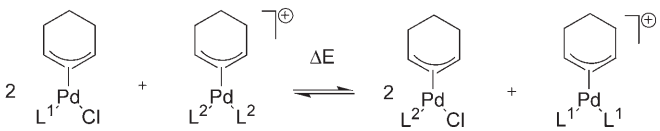

Figure 8. Isodesmic equilibria between (η^3-cyclohexenyl)PdLCl and (η^3-cyclohexenyl)PdL_2 species, where L is PPh_3, PCy_3, $P(2\text{-BiPh})Cy_2$, and $P(t\text{-Bu})_3$.

involving the isolated chloride anion, we have invoked the following isodesmic equilibria: where L is PCy_3, $P(2\text{-BiPh})Cy_2$, or $P(t\text{-Bu})_3$.

$$\Delta E = E\{2(\eta^3\text{-allyl})PdPPh_3Cl + [(\eta^3\text{-allyl})PdL_2]^+\} - E\{2(\eta^3\text{-allyl})PdLCl + [(\eta^3\text{-allyl})Pd(PPh_3)_2]^+\} \quad (1)$$

The tendency to form the cationic, diphosphine-ligated allylpalladium complex can then be compared to the PPh_3 ligand for each of the other phosphine ligands in turn. Upon exchange of the phenyl groups for cyclohexyl the equilibrium is shifted from the diphosphine-ligated complex, which must be attributed to the larger steric demand of the unsaturated cyclohexyl substituents. The calculated energy difference according to Eq. (1) was 54 kJ mol^{-1}.

For the $P(2\text{-BiPh})Cy_2$ ligand the difference in energy compared to PPh_3 was surprisingly small (only 21 kJ mol^{-1}) which could be due to this particular conformation of the diphosphine-ligated allylpalladium complex. The conformation is stabilized by C–H π interactions between the two biphenyl groups, thus resulting in an overall energy which may not represent the true distribution of conformations present at room temperature. This is underlined by inspection of the conformational searches performed using molecular mechanics, where the distribution of low-energy conformations is much more narrow for $P(2\text{-BiPh})Cy_2$ compared to PPh_3. Here the difference between the energy of the single lowest energy conformation and the energy for the entire ensemble of structures generated during the conformational search is a good measure of the "conformational entropy".[20]

In molecular mechanics the cationic allylpalladium complex incorporating two extremely sterically encumbered $P(t\text{-}Bu)_3$ ligands was also investigated, but in the following quantum mechanical structural optimization one of the ligands dissociated. This is a strong indication that for this particular ligand the diphosphine-ligated complex simply cannot form.

To estimate the difference in reactivity between the two allylic termini, an ammonia probe nucleophile was used and the energies for the two isomeric transition states compared (for additional information on the computational procedure, see Computational Details). In all cases but one the C–N distance was between 2.05 Å and 2.10 Å, indicating that there was little variation along the reaction coordinate (the TS has approximately same degree of early/late character). With PPh_3 as phosphine ligand the energy difference is large, 16 kJ mol^{-1}, indicating that in the absence of isomerization and alternative reaction pathways the product is expected to arise *only* from addition *trans* to phosphorus (Figure 9).

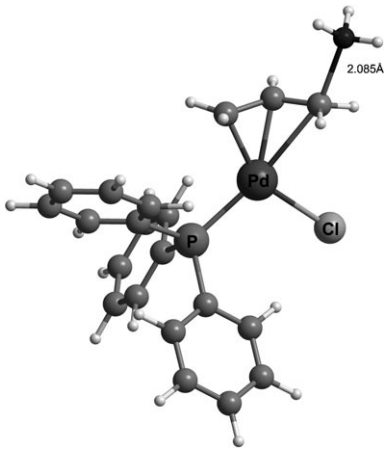

Figure 9. Structure of the TS for nucleophilic addition *trans* to phosphorus with PPh_3 as phosphine ligand.

With the PCy_3 as phosphine ligand the energy difference for the two isomeric transition states is merely 6 kJ mol^{-1} (Figure 10), which is particularly interesting when one recalls that this phosphine ligand exerted the largest structural distortion of the allyl complex in the ground-state (*vide supra*). At room temperature the calculated energy difference of 6 kJ mol^{-1} should result in a ratio of about 10:1 in favour of addition *trans* to phosphorus, and the observed lower enantiospecificity suggests that also for this phosphine ligand additional isomerization processes take place.

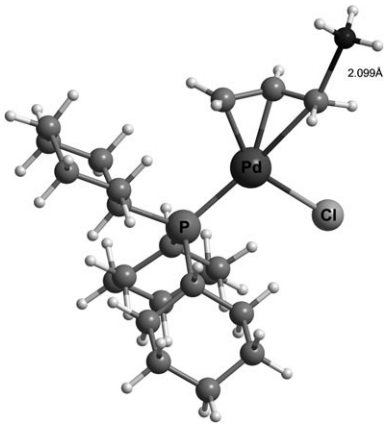

Figure 10. With cyclohexyl substituents on phosphorus the most favourable TS again results from nucleophilic addition *trans* to phosphorus.

For the isolated allyl complex having P(2-BiPh)Cy_2 as phosphine ligand the conformation with the biphenyl proximal to the allyl moiety was found to be slightly more energetically favourable (by 14 kJ mol^{-1}). The incorporation of implicit solvation lowered the energy difference to 5 kJ mol^{-1}, which prompted us to investigate all four possible isomeric transition states (Figure 11).

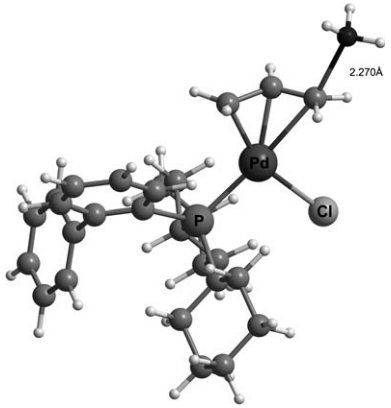

Figure 11. The conformer of TS with the biphenyl moiety oriented away from the allyl group has the lowest energy of the four possibilities (*trans* to P/Cl, biphenyl proximal/distal).

As expected, the two most favourable reaction pathways were both *trans* to phosphorus, but to our surprise the conformer with the biphenyl moiety pointing away from the allyl was found to be slightly lower in energy (5 kJ mol^{-1}), which is opposite of what was found for the ground state complexes. For the two TS determined for reaction *trans* to chloride the one having the biphenyl moiety proximal to the allyl was favoured (relative energy 21 kJ mol^{-1} *vs.* 30 kJ mol^{-1} for the distal isomer). The possibility for the biphenyl moiety to interact closely with the allyl moiety could be the reason for the relatively high memory effect observed with this ligand since many isomerization pathways are blocked or at least hindered.

Finally, we have also used the ammonia probe to study the inherent memory effect with P(*t*-Bu)$_3$ as phosphine ligand (Figure 12). Here the energy difference between the competing transition states was 9 kJ mol^{-1}, a moderate value which is higher than that observed for PCy_3 but lower than that observed for

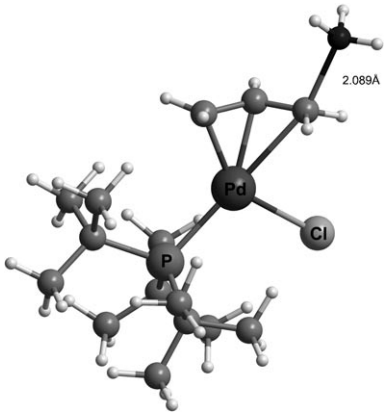

Figure 12. With the sterically encumbered P(*t*-Bu)$_3$ ligand the most favoured TS is the one resulting from addition *trans* to phosphorus.

PPh_3. With two phosphine ligands present the resulting allyl complex underwent ligand dissociation upon energy minimization, which strongly suggests that the "traditional" cationic pathway is not feasible for this phosphine ligand.

Discussion

Based on the structural features of the isolated η^3-(cyclohexenyl)allyl one would expect the largest memory effect to be exerted by the PCy_3 ligand, but this does not take into account the possibility for isomerization. Furthermore, the difference in bond lengths to each of the allylic termini does not necessarily correlate (in a straightforward manner) to the reactivity towards incoming nucleophiles. This is most clearly seen for the P(*t*-Bu)$_3$ ligand where the steric influence of the ligand distorts the allyl moiety in such a way that the bond *trans* to chloride is the longer one. The same is true, albeit to a lesser extent, for the other phosphine ligands and consequently we will base the following discussion on the relative energies of the two isomeric transition states only.

The (η^3-allyl)PdPPh_3Cl precatalyst has a high theoretical enantiospecificity and the low observed enantiospecificity is due to the intervention of alternative processes, most likely the presence of an equilibrium between this precatalyst and [(η^3-allyl)Pd$(PPh_3)_2$]$^+$ and apparent rotation around the η^3-allyl bond.

According to the calculated energy difference between the *trans* to P and *trans* to Cl transition states, (η^3-allyl)PdPCy_3Cl should afford lower enantiospecificity than (η^3-allyl)PdPPh_3Cl, but the experiments show the opposite. Reactions performed with various equivalents of PCy_3 or P(2-BiPh)Cy_2 relative to Pd and isodesmic equilibrium calculations suggest that this effect is due to higher lability of [(η^3-allyl)Pd$(PCy_3)_2$]$^+$ compared to [(η^3-allyl)Pd$(PPh_3)_2$]$^+$ Consequently, the equilibrium between [(η^3-allyl)Pd$(PCy_3)_2$]$^+$ and (η^3-allyl)PdPCy_3Cl lies towards (η^3-allyl)PdPCy_3Cl, which leads to a higher enantiospecificity.

Furthermore, (η^3-allyl)PdPCy_3Cl is the complex that shows observed enantiospecificity closest to the theoretically expected value. Obviously, competing processes such as isomerization of the η^3-allyl intermediate are slower for this catalyst.

Experiments and isodesmic equilibria calculations show that the (η^3-allyl)Pd[P(2-BiPh)Cy_2]$_2$ complex can form only to a very small extent because of van der Waals repulsions between the two ligands and the allyl, which exist in most of the conformations found by conformational search. In addition, the (η^3-allyl)PdP(2-BiPh)Cy_2Cl structure shows high theoretical enantiospecificity (>99%) as well as hindered isomerization of the η^3-allyl intermediate. One suggestion for the observed moderate enantiospecificity of 44% could be that (η^3-allyl)PdP(2-BiPh)Cy_2Cl is in equilibrium with the [(η^3-allyl)PdCl]$_2$ dimer; when (η^3-allyl)PdP(2-BiPh)Cy_2Cl is reformed by the addition of P(2-BiPh)Cy_2 the enantiospecificity is lost. As [(η^3-allyl)PdCl]$_2$ is catalytically inactive the presence of this equilibrium would also explain the slow reaction rate.

DFT calculations on (η^3-allyl)Pd[P(*t*-Bu)$_3$]$_2$ show that the structure is inherently unstable and cannot form because of van der Waals repulsions. The (η^3-allyl)PdP(*t*-Bu)$_3$Cl complex also suffers from several van der Waals repulsions, but the experimentally observed enantiospecificity implies that this complex can form. These van der Waals repulsions cause an elongation of the bond between Pd and the terminus of the allyl moiety *trans* to chloride. In spite of this there is still an electronic difference between the two ligands, which should yield enantiospecificity due to attack *trans* to phosphorus. As for the previous case with (η^3-allyl)PdP(2-BiPh)Cy_2Cl we assume that the low enantiospecificy and low reaction rate are due to equilibria involving the [(η^3-allyl)PdCl]$_2$ dimer.

Conclusions

The hypothesis that enantiospecificity (e.g., a memory effect) can arise from a catalytic cycle where Pd is ligated by one phosphine and one chloride ligand is in agreement with all results in the current study. As chloride is common in all Pd-catalyzed allylic alkylations where it has not been carefully excluded, this has strong implications for applications in asymmetric catalysis. In all cases where the substrate is a chiral but racemic allylic acetate, the observed enantioselectivity for any given ligand is expected to be lowered by the enantiospecificity observed here. This is particularly true for monodentate phosphine ligands, but

also for electronically unsymmetric ligands, whereas C_2-symmetric ligands binding in a bidentate mode, thereby enforcing reactivity *via* a cationic complex, should not suffer from this type of memory effect.

The enantiospecificity has been shown to be strongly dependent on reaction conditions. A number of dynamic equilibria, including apparent allyl rotation and ligand exchange, can break the *trans* relationship between phosphorus and the reactive site that is a requirement for the specificity. Due to these equilibria, the enantiospecificity is too low to be of practical use in any of the cases investigated, but it is still an effect that can interfere significantly in potentially selective Pd-catalyzed allylic allylations.

Experimental Section

2-Cyclohexen-1-ol of 95% *ee* was synthesized from racemic 2-cyclohexenyl methyl carbonate as described in the literature,[21,22] and then acetylated under standard conditions. The carbonate was synthesized from the commercially available racemic 2-cyclohexen-1-ol.[23]

Syntheses of (η^3-allyl)PdPPh$_3$Cl, (η^3-allyl)PdPCy$_3$Cl, (η^3-allyl)PdP(2-BiPh)Cy$_2$Cl, and (η^3-allyl)PdP(*t*-Bu)$_3$Cl from [(η^3-allyl)PdCl]$_2$ and PPh$_3$, PCy$_3$, P(2-BiPh)Cy$_2$, and P(*t*-Bu)$_3$, respectively, were based on a modified procedure of Powell et al.[11]

(η^3-allyl)PdPPh$_3$Cl and (η^3-allyl)PdP(2-BiPh)Cy$_2$Cl

[(η^3-allyl)PdCl]$_2$ (50 mg, 0.137 mmol) was dissolved in a minimum of dry warm benzene under argon and PPh$_3$ or P(2-BiPh)Cy$_2$ (0.260 mmol) was added and the reaction was left to stir for 10 min at room temperature under argon. The solution was stored at 4 °C until yellow crystals precipitated. The product was recrystallized from dry warm ethanol, which afforded (η^3-allyl)PdPPh$_3$Cl (mp 170–176 °C, dec.) or (η^3-allyl)PdP(2-BiPh)Cy$_2$Cl (mp 140–146 °C, dec.) as yellow crystals which were pure according to ^{1}H NMR spectroscopy.

(η^3-allyl)PdPPh$_3$Cl: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.76 (d, 1H, J = 12 Hz), 3.04 (d, 1H, J = 7 Hz), 3.70 (dd, 1H, J = 14, 10 Hz), 4.70 (td, 1H, J = 7, 2 Hz), 5.61 (1H, ddt, J = 14, 14, 7 Hz), 7.36–7.66 (m, 15H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 61.2 (s), 80.1 (d, J = 46 Hz), 118.3 (s), 128.7 (d, J = 16 Hz), 130.6 (s), 134.0 (s), 134.3 (s).

(η^3-allyl)PdPP(2-BiPh)Cy$_2$Cl: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.00–2.3 (m, 23H), 3.07 (m, 2H), 4.35 (m, 1H), 4.82 (m, 1H), 7.15–7.64 (m, 9H).

(η^3-allyl)PdPCy$_3$Cl and (η^3-allyl)PdP(*t*-Bu)$_3$Cl

[(η^3-allyl)PdCl]$_2$ (50 mg, 0.137 mmol) was dissolved in a minimum of dry warm benzene under argon and PCy$_3$ or P(*t*-Bu)$_3$ (0.260 mmol) was added and the reaction was left to stir for 10 min. at roomtemperature under argon. The solvent was removed by evaporation under vacuum and the product was recrystallized from dry warm EtOAc, which afforded (η^3-allyl)PdPCy$_3$Cl (mp 172–178 °C, dec.) or (η^3-allyl)PdP(*t*-Bu)$_3$Cl (mp 124–130 °C, dec.) as yellow crystals which were pure according to ^{1}H NMR spectroscopy.

(η^3-allyl)PdPCy$_3$Cl: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.12–2.20 (m, 33H), 2.58 (d, 1H, J = 12 Hz), 3.38 (d, 1H, J = 6 Hz), 3.55 (dd, 1H, J = 14, 9 Hz), 4.59 (t, 1H, J = 6 Hz), 5.38 (ddt, 1H, J = 20, 14, 7 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 26.5 (s), 27.7 (d, J = 16 Hz), 30.3 (s), 34.4 (d, J = 28 Hz), 51.1 (s), 80.4 (d, J = 43 Hz), 116.4 (s).

(η^3-allyl)PdP(*t*-Bu)$_3$Cl: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.52 (d, 27H, J = 12 Hz), 2.80 (d, 1H, J = 8 Hz), 3.81 (dd, 1H, J = 13, 8 Hz), 4.11 (br s, 1H), 4.72 (t, 1H, J = 7 Hz), 5.41 (ddt, 1H, J = 20, 13, 7 Hz).

Allylic Alkylations of 2-Cyclohexen-1-yl Acetate

The allylic alkylations of 2-cyclohexen-1-yl acetate were carried out following a modified procedure of Longmire et al.,[24] and the reaction mixtures analyzed by chiral GC using a Chrompack CP Chirasil-Dex CB capillary column (25 m × 0.25 mm × 0.25 μm).

The enolate ion was preformed by adding dimethyl malonate (70.6 mg, 0.534 mmol) to dry THF (1 mL) under argon followed by 1.0 M NaHMDS in THF (0.428 mL, 0.428 mmol) and the mixture was left to stir for 30 min. Separately, 2-cyclohexen-1-yl acetate (30.0 mg, 0.214 mmol) was added to dry THF (1 mL) under argon followed by the precatalyst (0.00641 mmol) and the solution of preformed enolate ion. The reactions were monitored and the enantiospecificity determined by chiral GC [100 °C for 12 min, then a ramp (20 °C/min) to 125 °C which was kept for 17 min, t_{R1} = 31.2 min, t_{R2} = 31.9 min].

The crude product was purified by flash chromatography to afford dimethyl 2-(2-cyclohexenyl)malonate as a colorless oil which was pure according to ^{1}H NMR spectroscopy. ^{1}H NMR: δ = 1.59 (m, 2H), 1.75 (m, 2H), 1.98 (m, 2H), 2.92 (m, 1H), 3.29 (d, 1H, J = 10 Hz) 3.74 (two s, 6H), 5.52 (dq, 1H, J = 10, 2 Hz), 5.78 (ddd, 1H, J = 10, 6, 3 Hz).

Computational Details

Molecular modeling was performed using the Maestro visualization software from Schrödinger Inc. v. 7.5 release 106.[25] The conformational space of the allyl complexes was investigated using the MM3* force-field,[26] which had been modified to also include the Pd-allyl moiety as described previously.[27] In addition minor adjustments were performed to allow the presence of the chloride ligand.

Initial conformational searches consisted of 1000 steps of a torsional search using the Monte Carlo Multiple-Minimum (MCMM) method,[28]] as incorporated in MacroModel v. 9.11 release 106. The global energy minimum was subjected to a new energy minimization using density functional theory (B3LYP)[29] in combination with the LACVP* basis set as implemented in Jaguar v. 6.5 release 106. LACVP* uses the 6–31G* basis set for all light elements and the Hay–Wadt ECP and basis set for Pd and Cl.[30] For the evaluation of the inherent reactivity ammonia was used as a probe nucleophile. For these studies a solvation model was found to be crucial, which was accomplished using the Poisson–Boltzmann self-consistent reaction field approach[31] as implemented in Jaguar v. 6.5 with parameters suitable for CH_2Cl_2 [dielectric constant (ε): 9.08, molecular weight (M_w): 84.93 and density (ρ): 1.3266].

The transition states were located as follows. First the structure of the Pd(0)-alkene product complex was determined, which in all cases had C–N bond lengths of approximately 1.6 Å. Then two minimizations were performed with a fixed elongation of the C–N bond length to either 2.0 Å or 2.5 Å, thus mimicking the transition state or pre-reactive allyl complex, respectively. With these three structures in hand a quadratic synchronous transit (QST) transition state search could be started. A QST-guided search is restricted along the circular curve connecting the reactant, transition-state guess and product structures in the beginning of the search, which should reduce the risk of ending up with false transition states. In all cases the initial, guessed Hessian was refined along the 3 lowest frequency eigenvectors, and the lowest Hessian eigenvector was followed.

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