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Coordination of the Trost modular ligand to palladium allyl fragments: Oligomers, monomers, and memory effects in catalysis*

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Abstract: Reaction of the C_2-symmetric "Trost modular ligand" with cationic Pd(II) allyl fragments allows isolation of air- and bench-stable procatalysts for the asymmetric allylic alkylation of racemic cycloalkenyl esters. In solution, three distinct complexation modes are observed. When mixed in a ligand/Pd ratio of 1/2, a binuclear bis-*P,O*-chelate complex is generated. This species does not induce enantioselectivity in the reaction. In contrast, with a ligand /Pd ratio of 1/1, a highly enantioselective, *P,P*-coordinated procatalyst system is generated in which there are two basic coordination modes: monomeric and oligomeric. The monomeric form is mononuclear and exists as two 13-membered chelates, isomeric through loss of C_2-symmetry in the ligand. The oligomeric form is polynuclear and forms chains and rings of alternating ligand and cationic Pd(allyl) units, one of which was identified by single-crystal X-ray diffraction. In solution, the monomeric and oligomeric species are in dynamic equilibrium with populations and interconversion rates controlled by concentration, temperature, and counterion. Isotopic desymmetrization analysis suggests that the monomer–oligomer equilibrium plays a crucial role in both the selectivity and efficiency of the asymmetric allylic alkylation reaction.

ASYMMETRIC Pd CATALYSIS WITH THE TROST MODULAR LIGAND

Since its introduction in 1992 by Trost, Van Vranken, and Bingel [1], the C_2-symmetric "Trost modular ligand" system (**1**) has been expanded and developed [2] to the point where it is undeniably one of the most successfully and broadly applied ligand classes in asymmetric transition metal-catalyzed C–C bond-forming reactions. Within the series, by far the most widely employed ligand is bis-amide **2** [3], which is easily prepared by reaction of *o*-(diphenylphosphino)benzoic acid [4] with commercially available enantiomerically pure *trans*-1,2-diaminocyclohexane.

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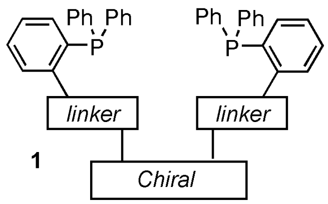

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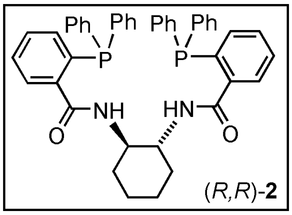
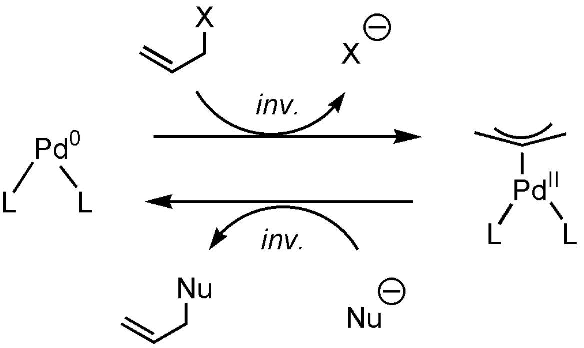


(*R*,*R*)-**2**

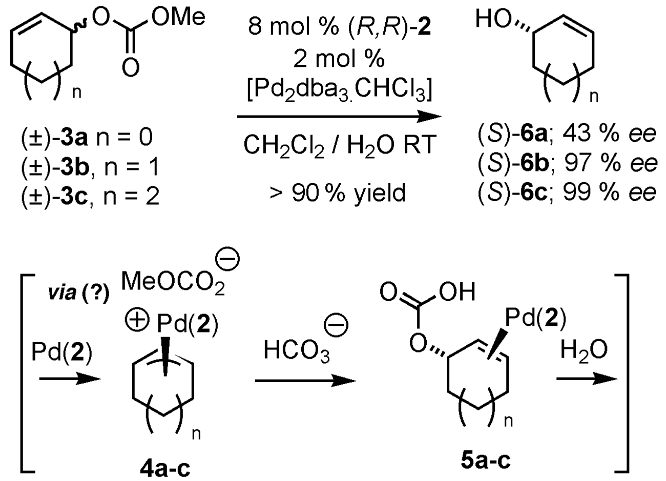
A wide variety of mid to late transition metals are known to catalyze the reaction of allylic electrophiles with carbon and heteroatom nucleophiles [5]. Within this broad range of reactions, the mechanism and associated stereochemistry of the Pd-catalyzed processes have been studied in most detail. Thus, it is well known that, in the majority of cases [6], reactions involving simple allylic electrophiles with stabilized nucleophiles proceed via an *inversion–inversion* sequence, involving a shuttle between Pd(0) and an η^3-allyl palladium (II) intermediate, Scheme 1.



Scheme 1

The allylic alkylation reaction presents the opportunity for a number of different modes by which chiral enantiomerically enriched ligands can be employed for asymmetric synthesis [5,7]. In particular, there is a growing range of ligands capable of inducing high enantioselectivity (>90 % ee) in the reaction of cyclic allylic substrates of genuine synthetic utility. These are significantly more challenging than the classic 1,3-diphenylpropenyl substrate, and it is with these cycloalkenyl ester substrates that the commercially available [8] "Trost modular ligand" system (**1**), especially the diaminocylohexane-based ligand **2**, has made such an impact. For example, (±)-cycloheptenyl methyl carbonate **3c** can be hydrolyzed in CH_2Cl_2/H_20 with 4 mol % Pd and 8 mol % **2** to give cyclohept-2-enol (**6c**) in 94 % yield and > 99 % ee possibly via hydrolysis of intermediate **5c**—or its [Pd(**2**)]-free analog—generated by near-perfect regioselectivity in the nucleophilic attack of the "meso"-π-allyl intermediate **4c** by hydrogen carbonate ion, Scheme 2 [3b].

The analogous reaction of the cyclopentenyl substrate **3a** affords **6a** in only 43 % ee. However, on switching from the methyl carbonate to the corresponding acetate/$KHCO_3$, the ee of the hydrolysis product (**6a**) increases to 88 %. At first inspection, the only difference between the two reactions is the counterion to the "meso"-π-allyl intermediate **4a**, and this is a good example of how, with ligand **2** in particular, subtle changes in the substrate or the reaction conditions can lead to surprisingly large differences in outcome.



Scheme 2

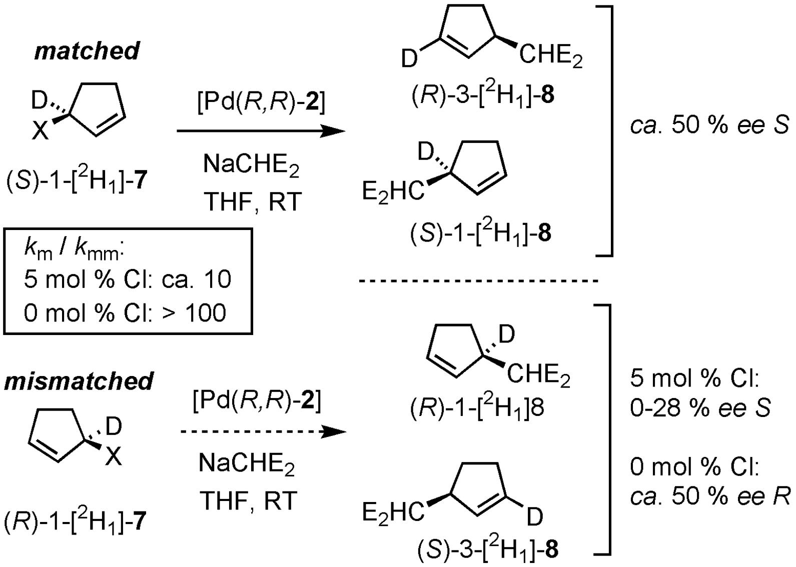
"MEMORY EFFECTS" AND RELATED "UNEXPECTED" PHENOMENA

Despite the wealth of mechanistic detail known about the Pd-catalyzed allylic alkylation reaction, there still remains a number of curious and not fully explained effects in this reaction type. A "memory effect" may be defined [9] as a situation in which isomeric allylic substrates (enantiomers, diastereoisomers, or regioisomers) react to give isomeric substitution products in ratios that depend upon the identity of the substrate, but where the classical mechanism predicts that there should be no such dependence. The first examples of these memory effects were reported by Fiaud and Malleron [10] in 1981, and recently there has been a resurgence of interest in mechanistic aspects of these phenomena and their potential for complicating the application of the reaction [11]. In most cases, memory effects are undesirable since they can attenuate the efficacy with which a chiral ligand is able to control the stereoselectivity of a process that involves a mixture of stereoisomeric substrates, most often a racemic substrate.

The mechanistic origins of memory effects remain unsatisfactorily explained in many cases. The simplest situation in which a stereochemical memory effect may arise is that in which enantiomeric substrates yield diastereoisomeric Pd-π-allyl intermediates that are unable to equilibrate in competition with nucleophilic attack. If the diastereoisomers give rise to different products or product ratios, then a memory effect is engendered. In the case of cyclopentenyl substrates (**7**), we have attempted to quantify such situations by introducing a *stereochemical convergence* (sc) term against which the global enantiomeric excess (ee_g) can be analyzed as a simple function [9]. 0 % sc means that the reaction of opposite enantiomers of substrate gives exactly the opposite outcome. As diastereoisomer equilibrium increases, the outcomes become more similar until at 100 % sc they are identical and there is no longer a memory effect. By deployment of a deuterium label (α-^{2}H-**7**) such that intermediates become isotopically desymmetrized [12] and by exploiting the stereospecific nature of the reaction (net retention, *inversion–inversion*, of stereochemistry), one may simultaneously determine, by ^{13}C NMR analysis of α/γ-^{2}H-**8**, the enantiomeric excesses arising from the individual substrate enantiomers and thus both ee_g and sc. Systems in which the memory effect arises from slow diastereoisomer equilibration, display a characteristic change in ee in *both* manifolds as the sc is modulated by changes in reactions conditions. A good example of this phenomenon is observed in the alkylation of cyclopentenyl esters (**7**) using the P,C/P,X ligands [13], "MAP" [14], and "MOP" [15].

Study of the analogous reaction catalyzed by Pd complexes bearing the Trost modular ligand **2** and employing the ^{2}H labeling technique described above, demonstrates that this system also displays a memory effect [11b]. However, the manner in which the two enantiomers of the substrate

[**7**; X = $MeCO_2$ (=**3a**), $PhCO_2$, *t*-$BuCO_2$, $MeOCO_2$] behave on changing the reaction conditions clearly indicates that the origin of the effect is more complex than the simple issue of relative rates of interconversion of diastereoisomeric Pd-π-allyl intermediates, vide supra. The key findings are outlined in Scheme 3 and may be summarized as follows. Firstly, there is extensive matching and mismatching between the catalyst system and the two enantiomers of substrate. Under the "classic" reaction conditions employing THF as solvent, (*R*,*R*)-**2**/[Pd(allyl)Cl]$_2$ as procatalyst and an excess of $NaCHE_2$ (E = CO_2Me) as nucleophile, there is a relatively efficient kinetic resolution (*s* > 10). The faster-reacting matched enantiomer (S)-**7** gives rise to (*S*)-**8** in ca. 50 % ee, independent of nucleofuge. In contrast, the slower-reacting mismatched enantiomer (*R*)-**7** gives **8** in a lower ee that is dependent on the identity of the nucleofuge. As the steric bulk is increased, the ee drops, and with pivalate (**7**, X = *t*-$BuCO_2$) the product (**8**) is essentially racemic.



Scheme 3

The effect of chloride ion, which is present through use of [Pd(π-allyl)Cl]$_2$ as procatalyst, is remarkable. Halide abstraction (Ag^+) before or during reaction, or use of a chloride ion-free source such as $Pd_2(dba)_3 \cdot CHCl_3$, reduces the relative rate of reaction of the mismatched substrate dramatically (*s* >> 100). Thus, matched (*S*)-**7** (X = *t*-$BuCO_2$) reacts smoothly and quantitatively within a matter of minutes and gives (*S*)-**8** in ca. 50 % ee (exactly the same as it does in the presence of chloride) and (*R*)-**7** is recovered in 30–50 % yield and > 90 % ee, providing that an excess of nucleophile is employed [16]. Nonetheless, (*R*)-**8** does undergo very slow reaction and after 5 days, is converted (ca. 45 %) to (*R*)-**8** (ca. 50 % ee). Control experiments employing *alkyl*^{18}O-labeled *rac*-[$^{18}O_1$]-**7** and enantiomerically pure samples of matched and mismatched [$^2H_1$]-**7** confirm that there is little or no reversible ionization or racemization under the reactions conditions and that it proceeds stereospecifically [11b].

The "Pd-**2**"-catalyzed reaction of cyclopentenyl esters (*rac*-**7**) under the classical conditions may therefore be described as enantiodivergent with the mismatched substrate unable to efficiently enter the selective manifold and thus predominantly reacting through an alternative and unselective manifold. The increased kinetic resolution selectivity (*s*) in the absence of halide suggests that chloride ion facilitates or catalyzes this competing unselective process. Further evidence for unusual behavior comes from the study of reaction kinetics, determined by microcalorimetry [17], for the alkylation of 0.1 M *rac*-**7** (X = O_2CPh) in THF at 25 °C with 2.5 equiv $NaCHE_2$ catalyzed by "Pd-**2**" [18]. It emerges that there is a nonlinear relationship between $[Pd]_{active}$ and $[Pd]_{tot}$ (where $[Pd]_{active}$ is the concentration of catalyst undergoing rapid turnover) with $[Pd]_{active}$ reaching a maximum when $[Pd]_{tot}$ is ca. 5 mM and then *decreasing* as $[Pd]_{tot}$ is further increased [19]. Similarly, unexpected phenomena have been observed in related reactions catalyzed by "Pd-**2**". For example, in the reaction of methyl (1,3-dimethylpropenyl) carbonate with the anion of nitroethane to generate *E*-4-methyl-5-nitrohex-2-ene, the asymmetric induction in the major diastereoisomer of latter is inversely dependent on catalyst loading. Hence, with $[Pd]_{tot}$ = 4 mol %, the product is obtained in 53 % ee, with 1 mol % this increases to 92 % ee and at 0.5 mol % selectivity rises to a remarkable 97 % ee [20,21].

MULTIPLE COORDINATION MODES IN THE COMPLEXATION OF THE TROST MODULAR LIGAND TO CATIONIC PD(II)-ALLYL FRAGMENTS

In order to address the above issues, we have studied the complexation of ligand **2** to Pd-allyl fragments, using the techniques of NMR, polarimetry, and X-ray crystallography. In all applications of ligand **2** described in the literature, the *P,P*-bidentate coordination of **2** to the Pd-allyl intermediate, through both Ph_2PAr units, to form a chelate (cf. **9**, vide infra) is proposed as the sole coordination mode [2a]. Due to the instability of Pd-π-cyclopentenyl species (β-H elimination spontaneously occurs and cyclopentadiene is generated) [9], we have studied the simplest acyclic system, Pd-π-allyl, as well as the more catalytically relevant cyclic system Pd-π-cyclohexenyl. Reaction of ligand **2** with $[Pd(\pi\text{-allyl})Cl]_2$ (**2**/Pd = 1) in CD_2Cl_2 or d_8-THF results in the generation of a mixture of complexes whose ^1H and $^{13}C\{^1H\}$ NMR spectra are essentially unassignable due to the broad and overlapping nature of the signals arising from numerous species. The $^{31}P\{^1H\}$ NMR spectrum is somewhat simpler (Fig. 1, spectrum **A**), however, even here, at least three major ^{31}P environments are evident, all of which appear as singlets (23–26 ppm).

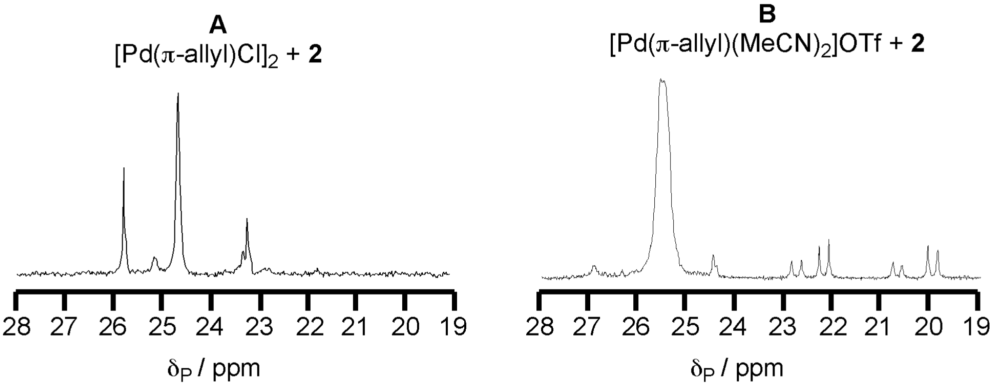
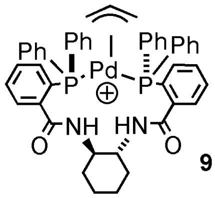


Fig. 1 $^{31}P\{^1H\}$ NMR spectra (162 MHz) of complexes generated in situ from ligand **2** and two different Pd-allyl sources in CD_2Cl_2. Spectrum **A**: mixture of complexes obtained from $[Pd(\pi\text{-allyl})Cl]_2$ (**2**/Pd = 1); Spectrum **B**: mixture of complexes obtained from $[Pd(\pi\text{-allyl})(MeCN)_2]OTf$ (**2**/Pd = 1). See text for full discussion.

A coordination mode of type **9** would be expected to give rise to a simple $^{31}P\{^1H\}$ NMR spectrum: on complexation to the "C_1" Pd-allyl fragment, the two phosphines in C_2-symmetric **2** become inequivalent (P_A and P_B). Scalar coupling between the two *cis*-related P nuclei through the Pd (i.e., $^{2Pd}J_{PP}$) should then result in a *single* pair of doublets if $\delta_{PA} \neq \delta_{PB}$ and a simple apparent singlet if $\delta_{PA} = \delta_{PB}$. It is important to note that the C_2-symmetry of **2** means that π-allyl rotamers (**9** and **9′**) are degenerate and thus a single complex should be generated. When a halide-free Pd(II) allyl source such as [Pd(π-allyl)(MeCN)$_2$][OTf] is employed, the ^{31}P{^{1}H} NMR spectrum is somewhat more informative (Fig. 1, **B**) with the emergence of *two* small pairs of doublets between 19.5 and 23 ppm (J = 33 Hz in both the major and minor pairs), in a nonequal population together with broad and uncharacterized peaks at 25–26 ppm [21]. However, the ^{1}H and ^{13}C NMR spectra remain complex and, as with the sample generated from [Pd(π-allyl)Cl]$_2$, there are no signals between –8 and –10 ppm in the ^{31}P{^{1}H} NMR spectrum which would correspond to noncoordinated Ph$_2$PAr units. Removal of the solvent affords an amorphous pale yellow powder that is air- and bench-stable and is a highly active procatalyst for *enantioselective* alkylation of cyclopentenyl esters. The powder dissolves in CD_2Cl_2 to give the same complex mixture (by ^{31}P{^{1}H} NMR). When the ratio of **2**/Pd is reduced from 1 to 0.5 by addition of a further 1 equiv of [Pd(π-allyl)(MeCN)$_2$][OTf], rapid conversion of the mixture to a new complex occurs and **10** can be isolated in essentially quantitative yield [16].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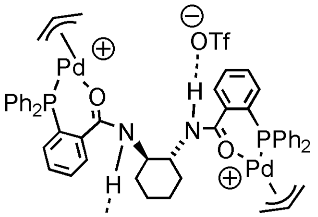
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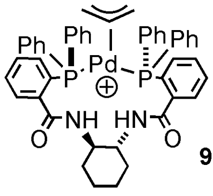
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The binuclear bis-P,O-chelation complex (**10**), which has been characterized in solution and also in the solid state (X-ray), is also an active procatalyst system for the alkylation of cyclopentenyl esters. However, it induces essentially no enantioselectivity (ca. 2 % ee) in the reaction of either enantiomer of substrate; nor does it effect their kinetic resolution [16]. Furthermore, on reestablishment of **2**/Pd = 1, complex **10** is reconverted to the mixture of complexes described above (Fig. 1, **B**). Since nearly all applications of **2** in catalysis employ 1.5 ≥ [**2**/Pd] ≥ 1 and high turnover rates are observed, it seems unlikely that the binuclear bis-P,O-chelated system **10** is the active species in these reactions [22].

So, what coordination modes are present in the mixture of complexes obtained with a Pd/**2** ratio of 1 under chloride-free conditions? A key observation is that on changing the temperature or, more importantly, the concentration, the ratio of species observed in the ^{31}P{^{1}H} NMR spectrum changes. At low concentrations (≤10 mM), the major and minor pairs of doublets are favored over the other species at 25–26 ppm. Such behavior suggests that higher-order species are generated at higher concentrations and at lower temperatures, i.e., $(M)_n$ is in equilibrium with $(M)_{n+x}$, and oligomerization is occurring. The simple pairs of double doublets between 19.5 and 23 ppm suggest these to be lower oligomers, perhaps even the monomeric species $(M)_1$, albeit as two isomeric forms. A clarification of this issue is discussed later. Using standard ^{31}P{^{1}H} NMR/serial dilution experiments to analyze the relationship between the degree of oligomerization and the total concentration for a series of complexes prepared in situ by reaction of [Pd(π-allyl)(MeCN)$_2$][X] with **2**, it is found that simple statistical relationships are obeyed when the total concentration of all species is relatively low [23]. Above a critical concentration, there is an increasing negative deviation of $[Pd]_{mon}$ from the predicted curve such that ultimately $[Pd]_{mon}$ falls as $[Pd]_{total}$ is increased. See, for example, the predicted and observed relationships for $\{[Pd(\pi\text{-allyl})(\mathbf{2})][SbF_6]\}_n$ in Fig. 2.

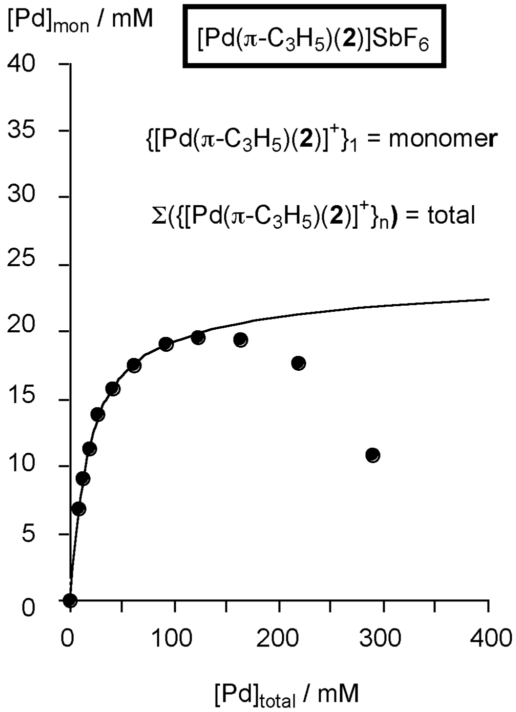
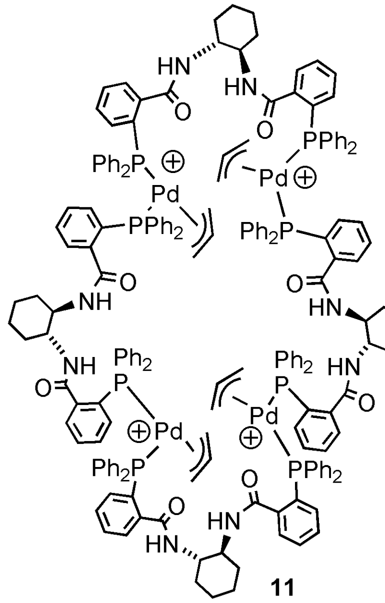


Fig 2 Graph showing the relationship between absolute concentration of the monomeric ionic species [Pd(π-allyl)(**2**)]SbF_6 (*y*-axis, $[Pd]_{mon}$/mM) and the total concentration of species {[Pd(π-allyl)(**2**)][SbF_6]}$_n$ (*x*-axis, $[Pd]_{total}$/mM) in CD_2Cl_2 at 23 °C. Data points, by serial dilution and $^{31}P\{^1H\}$ NMR analysis. Smooth curve: simulated relationship based on statistical model (which fits below $[Pd]_{total}$ = ca. 100 mM).

The obvious similarity to the kinetic studies outlined above suggests that higher-order oligomeric species are catalytically less active than the lower oligomers/monomeric species [24]. It is of note that the counterion to these complexes ([X]) has an important role in controlling oligomerization rates and equilibria [25]. With more "interactive" counterions (i.e., those more able to coordinate, ion-pair or hydrogen bond), oligomerization is more favorable and more rapid, cf. Fig. 1, **A** and **B** [24]. Furthermore, the cycloalkenyl unit is more sterically restrictive than a simple allyl unit and might be expected to further bias equilibrium against the monomeric species. In our model systems, this indeed this is found to be the case [25].

A MONOMERIC CHELATE AND A TETRANUCLEAR CYCLIC OLIGOMER

Despite many attempts, we have been unable to crystallize any complex from the mixture of monomeric and oligomeric complexes generated by reaction of enantiomerically pure ligand **2** with [Pd(π-allyl)$(MeCN)_2$][X], where **2** Pd = 1 and X = various "noncoordinating" ions. However, by employing *rac*-**2** and by careful optimization of its reaction with [Pd(π-allyl)$(MeCN)_2$][OTf], we were finally able to grow crystals [25,26]. These crystals proved very "fragile" with respect to loss of solvent, but were ultimately mounted successfully and single-crystal X-ray diffraction revealed them to be a tetranuclear complex (**11**) $[(Pd(\pi\text{-allyl}))_4(\mathbf{2})_4][OTf]_4\cdot(C_2H_2Cl_4)_x$ [27]. It should be noted that **11** is just a single component of a highly complex series of linear and cyclic oligomeric species that are interconverting reasonably rapidly in solution.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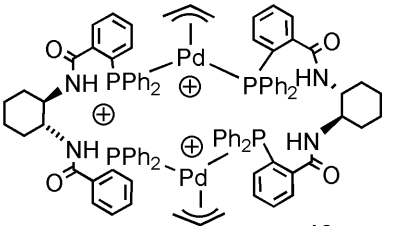
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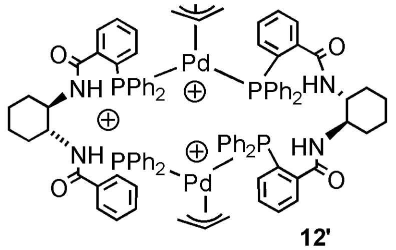
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Polarimetric studies on equilibrium mixtures of $\{[Pd(\pi\text{-allyl})(\mathbf{2})][OTf]\}_n$ in CH_2Cl_2 between 3 and 20 mM demonstrates that $[\alpha]_D obs$ correlates linearly with mol fraction monomer. The non-zero gradient indicates that the monomer and oligomer have different specific optical rotations, and the linearity suggests that the individual oligomers $\{[Pd(\pi\text{-allyl})(\mathbf{2})][OTf]\}_n$ have specific optical rotations that are essentially independent of "*n*". Extrapolation to mol fraction monomer = 100 yields the *intrinsic* optical rotation of the monomer $\{\alpha\}_D = +644$ and, by a similar process, extrapolation to 0 yields $[\alpha]_D = -151$ for the oligomeric species. From this data, it can be concluded that the monomeric species is not simply aggregated to form oligomers, but is fundamentally altered on oligomerization and also that the repeat components in the oligomer behave as independent units of optical activity, in accordance with the van't Hoff principle of optical superposition. Both features strongly suggest that oligomerization involves growth of chains and/or rings where each ligand (**2**) coordinates two separate cationic Pd-allyl units and the 1,2-diaminocyclohexane stereogenic centers communicate poorly with the triarylphosphino units.

The C_2-symmetry of the ligand (**2**) in monomeric chelate **9** should make π-allyl rotamers degenerate and thus a *single* pair of doublets should be observed in the $^{31}P\{^1H\}$ NMR spectrum. In contrast, in a homochiral cyclic dimer, only two of the three π-allyl rotamers (diastereoisomers) would be degenerate, thus there would be two isomeric species (see **12** and **12′**)—exactly what is seen in the $^{31}P\{^1H\}$ NMR spectrum (Fig. 1, **B**). Moreover, variable temperature $^{31}P\{^1H\}$ NMR studies on $\{[Pd(\pi\text{-allyl})(\mathbf{2})][OTf]\}_n$ in CD_2Cl_2 between –75 and 25 °C yields a linear van't Hoff relationship for the equilibrium between the isomeric lowest-order species ($\ln K_{eq} = (221 \pm 2.9/T) - 0.283 \pm 0.01$; $r^2 = 0.999$) and confirms they are of similar entropy ($\Delta S° = 2.4 \pm 0.1$ J K^{-1} mol^{-1}). To address the issue of whether or not the lowest-order species are isomeric forms of a mononuclear chelate (cf. **9**) or a higher-order species such as the cyclic dimers (**12** and **12′**), we prepared ligand d_{10}-**2** in which isotopic desymmetrization [12] is achieved by the perdeuteration of both phenyl groups on one of the Ph_2P units. This desymmetrization perturbs the NMR spectra of the resulting complexes because the two C_6D_5 units exert a significant net isotope shift (Δδ ca. –0.5 ppm) at the directly connected ^{31}P center with negligible perturbation of the other ^{31}P center or indeed the coordination behavior of d_{10}-**2** relative to **2**. By careful analysis of the cross-peaks in a $^{31}P^{31}P\{^1H\}$-COSY experiment conducted on a sample of $\{[Pd(\pi\text{-allyl})(d_{10}\text{-}\mathbf{2})][OTf]\}_n$ in CD_2Cl_2, we could then confirm that both of the pairs of doublets between 19.5 and 23 ppm correspond to the mononuclear chelate **9** [25]. A detailed study of the effect of the counterion on the equilibrium population and the rate and mode of interconversion of the isomeric forms of [Pd(π-allyl)(**2**)][X] [25], suggests that ligand **2** must be conformationally oriented in the Pd-allyl complexes such that the C_2-symmetry is lost. A schematic representation of a change in conformation leading to isomeric π-allyl rotamers **9** and **9′** is shown in Fig. 3. This effect most likely stems from the large size of the chelate ring (13-membered), which undergoes partial folding to reduce angle strain, or to maximize a Pd/carbonyl oxygen interaction.

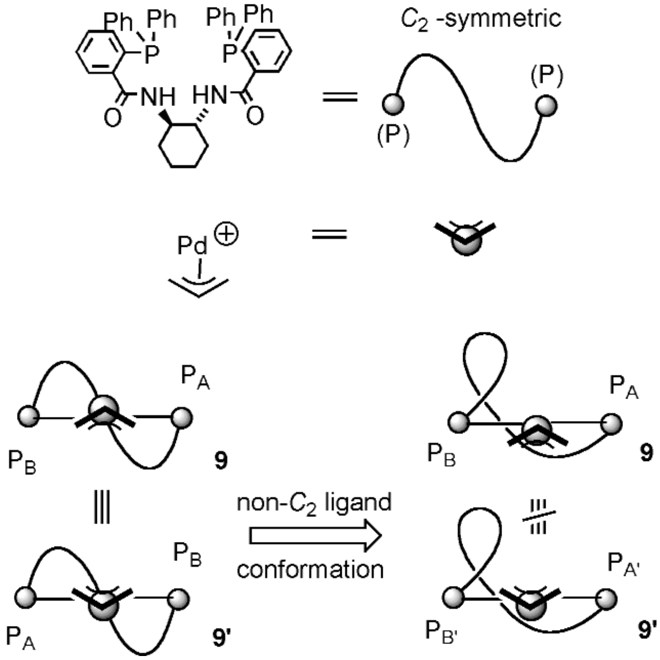
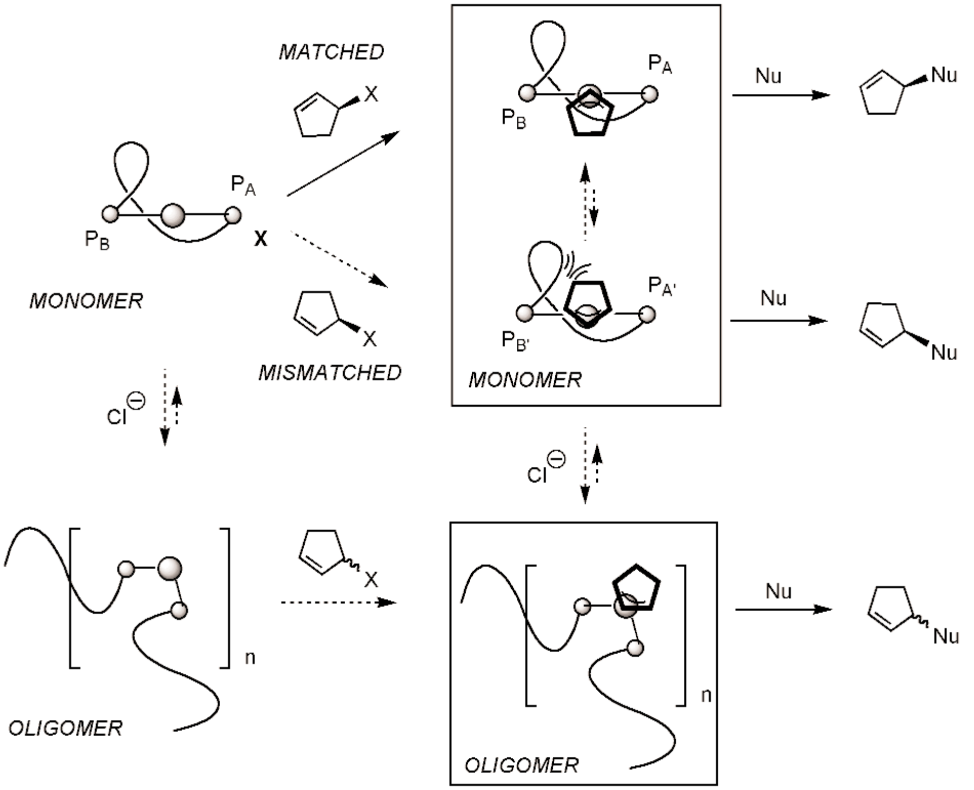


Fig 3 Schematic representation of the ligand symmetry in the mononuclear Pd-π-allyl chelate complex of ligand **2**, which has two isomers (π-allyl rotamers **9** and **9′**).

The small allyl group appears to exert little or no rotameric bias, as evidenced by 1/1 ratios of **9** and **9′** when "X" is noninteractive. With more interactive ions, the ratio is biased, presumably by ion-pairing with "X". However, on changing from a simple Pd-π-allyl group to the more sterically demanding Pd-π-cyclohexenyl group, the isomeric equilibrium is biased to such an extent that only one isomer is evident, irrespective of the nature of "X". This strong conformational bias resulting in a C_1-symmetric chelate may well be related to the mode by which asymmetric induction occurs, in contrast to the more conventional C_2-symmetric "flap" and "wing" model [20]. Indeed, this asymmetric blocking of an upper quadrant is directly analogous to the mode of operation of the highly enantioselective cymantrene-based ligand system developed by Helmchen [29].

A WORKING MODEL FOR THE ORIGIN OF "MEMORY", HALIDE, AND CONCENTRATION EFFECTS IN ALLYLIC ALKYLATION CATALYZED BY Pd(2)

Isotopic desymmetrization (^{2}H) of cyclopentenyl esters allows memory effects to be detected in their asymmetric alkylation reaction with $NaCHE_2$ (E = CO_2CH_3) catalyzed by "Pd-**2**" in THF or CH_2Cl_2, vide supra. Rather unusually, these memory effects cause the matched and mismatched enantiomers to behave very differently, such that the matched enantiomer reacts smoothly, in a chloride-independent manner, to give alkylation product **8** in 50–80 % ee, whereas the mismatched enantiomer requires chloride ion for reaction to proceed at a reasonable rate and gives **8** in low ee, which tends to be racemic as the size of the nucleofuge is increased. In the absence of chloride, a very slow reaction of mismatched (*R*)-**7** yields **8** in essentially the same ee as the matched substrate, but with the opposite configuration. Kinetic studies indicate that turnover rates in these reactions increase with increasing [Pd] until a limiting value is reached and then rates decrease. Our current working model involves the concept that there is a major difference in both selectivity (substrate recognition and asymmetric induction on nucleophilic attack) and activity between monomeric and oligomeric Pd-**2** species. This would apply to both Pd(0) and Pd(II)-allyl intermediates (and mixtures thereof in the oligomeric species), with the monomeric species being the more selective and active component in both cases. A simplified analysis of such a system comes by consideration of just two catalytic cycles, one involving chelated monomer and the other the complete set of linear and cyclic oligomers undergoing much slower turnover (on a [Pd] basis). Efficient chirality transmission from the central chirality of the cyclohexyldiamine moiety in **2** to the two triarylphosphine units at the non C_2-symmetric Pd center in the monomeric cycle results in selective recognition of matched substrate, thereby establishing a kinetic resolution. The slower-reacting mismatched substrate then competitively enters the slower oligomeric manifold, Scheme 4.



Scheme 4

Of course, the matched substrate may also enter the oligomeric manifold and additionally the monomeric and oligomeric cycles are in dynamic equilibrium. However, whether a substrate is efficiently able to enter one manifold and emerge from the other will depend on the rate of nucleophilic attack vs. monomerization/oligomerization rates [30]. Chloride ion and higher catalyst loadings will result in increasing concentrations of oligomer with monomer reaching a maximum concentration and then decreasing again, Fig. 2. Thus, under ideal conditions the oligomeric manifold may act as an efficient “loading mechanism” through which the mismatched substrate may enter the monomeric manifold or by which π-allyl rotamers are equilibrated. With the appropriate nucleophile/solvent, etc., both enantiomers can then emerge from one of the two monomeric manifolds in equally high enantiomeric excess.

Central to the above argument is that the monomer is in equilibrium with the oligomer and that the monomer is more active than the oligomer. Our studies on the effect of concentration and counterion on the complexation mode of **2** to [(π-allyl)-Pd] and to [(π-cyclohexenyl)-Pd] units, vide supra, supports these two concepts. However, the third concept that is crucial in completing the model is that the oligomer must suffer inefficient chirality transmission between the central chirality of the cyclohexyldiamine moiety and the two triarylphosphine units at each Pd center. In effect, the ligand **2** would behave in an analogous manner to a ligand in which the two phosphine centers are linked by an achiral unit [32]. Supporting evidence for poor chirality transmission comes from the expectation that a diastereotopically correlated hexa-aryl array around a Pd-center would induce high optical rotatory power, as is indeed the case for the monomeric complex [Pd(π-allyl)(**2**)]OTf, which exhibits a large intrinsic rotation ($\{\alpha\}_D$ = +650 in CH_2Cl_2). In contrast, the oligomer displays a much lower rotation ($[\alpha]_D$ = –151 in CH_2Cl_2) which is independent of the degree of oligomerization. Moreover, this value is similar in magnitude to the specific rotation of the free ligand **2** ($[\alpha]_D$ = = 61, *c* = 2.3, CH_2Cl_2) and the binuclear complex **10** ($[\alpha]_D$ = 38, *c* = 0.1, CH_2Cl_2), which induces very low selectivity in asymmetric allylation reactions.

CONCLUSIONS AND OUTLOOK

As has become evident from the numerous optimization studies by Trost et al. [2], and the results outlined herein, asymmetric Pd-catalyzed allylic alkylation employing ligand **2** can be very “sensitive” to reaction conditions. The ligand system is unusual in its chelate size, forming a 13-membered heteroatom ring, and in its very high enantioselectivity in the allylation reactions of substrates that are often considered “problem” substrates with other ligand systems. Furthermore, the ligand performs rather poorly with the more classic bulky linear substrates, such as the 1,3-diphenylpropenyl systems, that are readily alkylated with high selectivity by ligands forming more conventional chelate ring sizes. These results suggest that the large chelate ring plays an important role in the establishment of a small and well-defined correlated hexa-aryl array around the Pd reaction center within which there is an opportunity for torquoselective control of compact cyclic allylic moieties. Moreover, the asymmetry of this control may be related to the non-C_2 symmetric ligand conformation which then blocks an upper quadrant [29]. The two isomers of the monomeric chelate undergo dynamic equilibrium with linear and cyclic oligomeric species, as evidenced by NMR and X-ray crystallographic studies [25,27,28]. Such oligomeric species are proposed to be less active and less selective than the monomeric chelate, and low concentrations and higher temperatures bias this equilibrium toward the monomeric chelate. In the presence of chloride, the major origin of “memory effect” in this system is proposed to be the monomer–oligomer equilibria, which is exacerbated by the more bulky Pd-π-cycloalkenyl group as compared to the model unsubstituted allyl system. Of note is the observation that anion concentration, or ionic strength, and the degree of ion-pair dissociation cause the monomer–oligomer equilibrium to deviate from a simple statistical distribution model resulting in maxima in monomer concentrations rather than limiting concentrations independent of total concentration above a threshold value. Taken together, these results suggest that, generally, the conditions that will favor highest selectivity will involve low concentrations of catalyst, under conditions of low ionic strength. Furthermore, enantioselectivity may be decreased at lower temperatures, as has been observed in a number of cases [33].

Having established that monomer–oligomer equilibria are likely to play a key role in memory effects and related phenomena with ligands of type **2**, and also that the mononuclear chelate, which has two isomeric forms, is the selective component in the catalytic milieu, our primary goal is now to characterize the monomer—both in solution and in the solid state.

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19. These observations are consistent throughout the *whole* reaction evolution including the induction period and at no stage is there any darkening or Pd-black precipitation. Pd(0) metal (nano) particle aggregation/precipitation as has been reported for other systems: M. Tromp, J. R. A. Sietsma, J. A. van Bokhoven, G. P. F. van Strijdonck, R. J. van Haaren, A. M. J. van der Eerden, P. W. M. N. van Leeuwen, D. C. Koningsberger. *Chem. Commun.* 128 (2003).
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22. The mixture of complexes of the form $\{[Pd(\pi\text{-allyl})(\mathbf{2})][X]\}_n$ that is generated from **2** and cationic Pd-allyl sources is sufficiently reactive to effect mono- and bis-allylation of free ligand **2**, thereby co-generating Pd(0)(**2**). This reactivity mode becomes more apparent when X is interactive, A. Martorell, G. C. Lloyd-Jones, unpublished results.
23. The equations derived by Gray [D. C. Smith, G. M. Gray. *Dalton Trans.* 677 (2000)] can be applied at concentrations of $[Pd]_{tot}$ below a critical value ([X]-dependent).
24. Addition of common ion (as NaX) to solutions of $\{[Pd(\pi\text{-allyl})(\mathbf{2})][X]\}_n$ results in increasing oligomerization. This factor will extensively promote oligomerization in the catalytic allylic alkylation reaction medium.
25. I. J. S. Fairlamb, A. Martorell, P. M. Tomlin, J. M. Fernandez, T. Guerziz , G. C. Lloyd-Jones. Unpublished results.
26. The relationship % olig = {0.121[ee **2**, (%)]} + 55.6 was established, suggesting slightly higher stability of homochiral oligomers. The difference in solubility between enantiomerically pure and racemic samples is remarkable, with the former soluble to >200 mM and the latter <5 mM.
27. The full description of the structure and the X-ray diffraction analysis will be published elsewhere. I. J. S. Fairlamb, A. Martorell, J. C. Jeffery, T. Riis-Johannessen, G. C. Lloyd-Jones, unpublished results. It is of note that in **11**, homochiral pairing around the meso tetranuclear ring facilitates a complex network of hydrogen bonding that involves the triflate bridging amides between separate rings.
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