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NMR Spectroscopy

Determination of the Conformation of the Key Intermediate in an Enantioselective Palladium-Catalyzed Allylic Substitution from Residual Dipolar Couplings**

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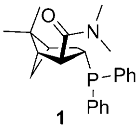
Transition-metal-catalyzed enantioselective C–C bond-forming reactions such as allylic substitution are of great importance in academic research and industrial processes.[1] In investigating the origin of the stereoselection of such a reaction knowledge about the spatial relationships between the ligand(s), the transition metal, and the substrate is a crucial step.[2] If an intermediate can be isolated, the spatial structure of the intermediate can in principle be obtained either by X-ray crystallography or NMR spectroscopy. However, it should be pointed out here that the equilibrium conformation of the intermediate does not necessarily lead to conclusive insights on reactivity and selectivity, since that depends on whether an early or late transition state is involved in the formation of the product.[3,4]

Extensive studies have been devoted to probing the origin of stereoselection in allylic substitutions with bidentate ligands, of which only few can be mentioned here.[5–14] For systems with monodentate ligands,[15–21] as is the case in the present study (see **1**), several X-ray structures of catalyst–substrate complexes exist, but to our knowledge no detailed NMR spectroscopic study in solution has yet been performed. The conformation of an intermediate complex in solution might not necessarily resemble that determined crystallographically. Furthermore, the solution conformation and in particular the dynamics of the intermediate species might be important for insight into the stereoselective step.



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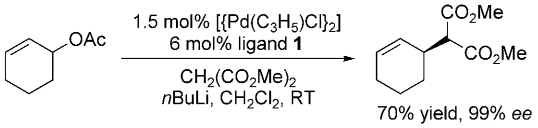
Unfortunately, determining the predominant conformation in solution is not always straightforward, especially if organometallic species are considered. Conventional NMR parameters such as ^3J couplings and NOEs might fail either because of missing links between spins (for both ^3J couplings and NOEs), missing parametrizations (for ^3J couplings especially for organometallic species), or conformational flexibility. This was also the case for the complex described herein.

In contrast to the short-range information content of ^3J couplings and NOEs, residual dipolar couplings (RDCs) provide long-range structural information and can also be used to relate non-interacting spins in biomolecular[22–30] and recently also in organic compounds.[31–46]

The complex investigated here by means of RDCs was reported by Helmchen et al. to be a self-organizing palladium catalyst system bearing two monodentate ligands **1** and showing high activity and enantioselectivity in allylic alkylation reactions (Scheme 1).[47–50] As the ligands are monodentate, considerable flexibility in the corresponding substrate–catalyst complex can be expected. It is thus very important to obtain information about the conformational behavior of the catalyst–substrate complex **2** in solution.



Scheme 1. Enantioselective allylic alkylation as described by Helmchen et al.[47,48]

To determine the conformation in solution we first searched for possible diastereomorphous complex conformations computationally.[51] We then determined intramolecular distances from NOE measurements. Unfortunately, only six nontrivial NOE contacts could be quantified using transient one-dimensional NOE spectroscopy (Figure 1).[52,53]

If one compares the NOE-derived distances with those obtained from computed complex conformations one cannot identify a single conformer that fits best (see Table SI3 in the Supporting Information). Thus, only a preselection of diastereomorphous complex conformations was possible on the basis of NOE data, leaving three possible conformations **A**, **B**, and **C**, which are in agreement with the NOE restraints (Figure 2). The task now was to distinguish whether the intermediate **2** displays a preference for one particular diastereomorphous complex conformation (**A**, **B**, or **C**) in solution. Alternatively, conformational flexibility could in

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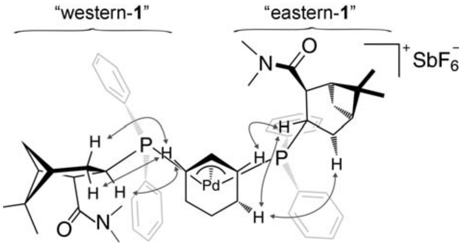

Figure 1. Catalyst–substrate complex **2** investigated and available non-trivial NOE contacts (indicated by arrows). Phenyl groups are shown in gray for clarity.

principle also lead to the interconversion between the conformers. To resolve these ambiguities, we decided to use RDCs, since they provide global information about the spatial relationship of moieties.

To obtain RDC data we needed the air- and moisture-sensitive intermediate **2** to be oriented in an anisotropic environment. At this stage two experimental features were crucial: All manipulations were performed under inert gas to prevent decomposition, and the degree of order induced had to be controlled precisely to obtain RDCs of appropriate magnitude. Both requirements were fulfilled using high-molecular-weight poly(γ-benzyl-L-glutamate) (PBLG) in CD_2Cl_2, which we recently showed to be superior to the commercially available low-molecular-weight PBLG.[54] The sample was prepared as follows: The complex was synthesized[47–50] directly in CD_2Cl_2, which had been dried using CaH_2. This solution was added to high-molecular-weight PBLG, which had been lyophilized twice from anhydrous benzene. After preparation of the liquid-crystalline phase its stability and homogeneity and the identity of the complex was verified by ^{2}H NMR spectroscopy (Figure SI 1) and $^{31}P\{^1H\}$ NMR spectroscopy (Figure SI 2), respectively. Full experimental details are given in the Supporting Information.

RDCs were extracted from CLIP-HSQC spectra[55] with additional decoupling of phosphorus in both dimensions (Figure 3). RDCs were calculated using Equation (1), where

$$D = (T - J)/2 \tag{1}$$

T is the total coupling constant extracted from spectra of the anisotropic solution and J is the corresponding scalar coupling constant obtained under isotropic conditions. Assignment of the resonances was unproblematic even in the anisotropic environment, with the exception of the diastereotopic protons 58 and 59 (atom numbering is given in the Supporting Information). These are the protons at the 4-position of the cyclohexenyl ring. Given that their corresponding dipolar couplings are essentially identical, a distinct assignment is not necessary.

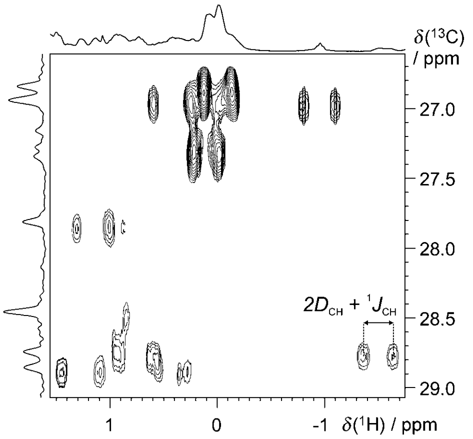

Figure 3. Section of the CLIP-HSQC$\{^{31}P\}$ NMR spectrum of **2** in a liquid-crystalline phase consisting of 9.5 wt% PBLG/CD_2Cl_2 recorded at 300 K.

To investigate whether the alignment medium influences the conformational equilibrium, we compared the chemical shifts in the isotropic and anisotropic phases (see Tables SI 1 and SI 2 in the Supporting Information). Apart from a constant shift of the resonances ($\Delta\delta = 0.6$ ppm in ^{13}C and $\Delta\delta = 1$ ppm in ^{1}H), these are essentially identical. Furthermore we compared long-range coupling constants determined in the isotropic phase with the corresponding coupling constants obtained in the anisotropic phase under magic angle sample spinning (MAS) conditions (Tables SI 5 and SI 6 in the Supporting Information). In this experiment the isotropic couplings are obtained in the anisotropic medium. The values obtained were essentially identical. Thus we have no indication for a conformational change induced by the liquid-crystalline phase. This is also in agreement with our recent investigation on the conformational equilibrium of an α-methylene-γ-butyrolactone.[46]

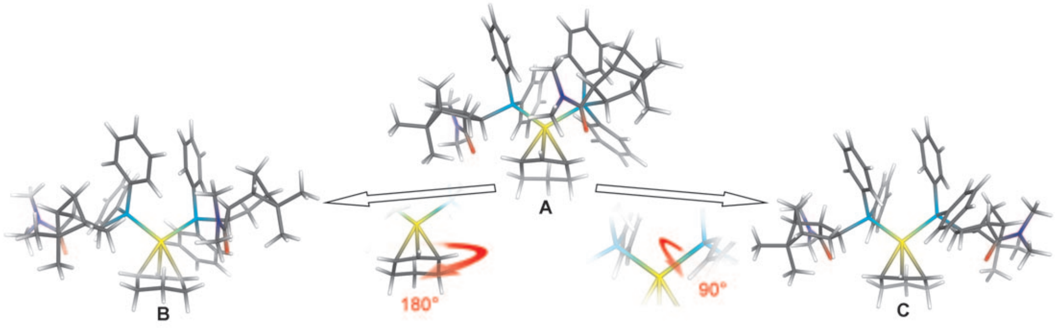

Figure 2. Diastereomorphous complex conformations of **2** that do not violate NOE restraints. Conformers **B** and **C** are obtained from **A** by either a 180° turn of the cyclohexenyl substrate (**B**) or a roughly 90° rotation of "eastern-**1**" (**C**) around the Pd–P bond with respect to conformer **A**. Atom coordinates of the equilibrium structures are given in the Supporting Information.

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To distinguish between the different diastereomorphous complex conformations **A, B**, and **C**, the dipolar coupling data was subjected to fitting procedures using a module of hotFCHT that we had developed.[56,57] The graphical result is depicted in Figure 4. The fit for the proposed structure **A** is significantly better than that for both **B** and **C**, leading us to reject the latter ones. But with a root mean square deviation of 6.77 Hz, the fit obtained for conformer **A** is still not satisfactory. This could either indicate flexibility within the whole complex or within certain moieties.

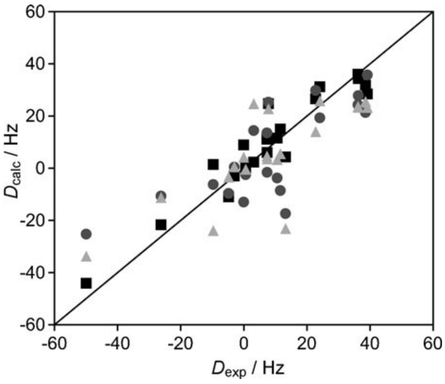

Figure 4. Comparison of the measured RDCs (D_{exp}) with the back-calculated values (D_{calc}). Squares: **A**, circles: **B**, triangles: **C**. The complete dataset resulting from fitting procedures and experimental RDCs can be found in the Supporting Information (Table SI 7).

To gain further insight into the reasons for the rather poor fit and to find out whether **A** can serve as a good representation of the conformation of **2** in solution, we subdivided **2** into three entities in our analysis. The three moieties ("eastern-**1**", "western-**1**", and the cyclohexenyl fragment) on Pd were considered as discrete units, and the fitting procedure was repeated for each individual unit. As only a very limited number of RDCs is accessible for each unit (six and seven, respectively), it is especially important to ensure that the RDCs used are linearly independent. This can be done by inspecting the rank (=5 for nonplanar fragments) and condition number of the directional cosine matrix of the alignment tensor.[28,62] The lower the condition number, the better defined the matrix, with 1 being the best possible condition number. As can be seen from Table 1, the condition numbers of the individual matrices are very low (2.5–3.7). Thus the individual order tensors can be determined reliably.

As expected, the dipolar couplings of the rigid myrthene-derived parts of ligand **1** showed excellent agreement with the back-calculated values (Table 1). The allylic domain, however, leads to a rather bad fit. This can be attributed to conformational flexibility, which was already indicated by the equal dipolar couplings of protons 58 and 59 (see above). This finding is also confirmed by the disorder of the aliphatic part of the cyclohexenyl ring in the X-ray crystal structure.[48]

Using this approach, values representing the quality of the fits are not sensitive to spatial relations of the moieties. Thus we must determine whether the flexibility of the allylic fragment is the only reason for the rather bad fit or whether the relative orientation of the ligands in solution is not correctly represented by structure **A**. The generalized degree of order ϑ for each unit (Table 1) and for the whole complex (fitting of all data to **A** leads to $\vartheta = 2.23 \times 10^{-3}$) are within the same range, which indicates that there is no difference in the (timescale of the) overall motion of the fragments with respect to each other. Thus we were encouraged to compare the orientations of the individual domains for structure **A**. If the spatial relation of the fragments in the corresponding structural proposal is correct, the orientation of each alignment tensor—which we refer to as the local order tensor—must be similar to the others. The applicability of this local order tensor technique for the determination of relative configurations in small molecules was demonstrated recently.[45]

Table 1: Statistical analysis of measured RDCs relative to back-calculated RDCs for each moiety (treated as discrete unit).[a]

	"western-**1**"	"eastern-**1**"	Allylic ligand
n[b]	7	6	7
RMSD[c] [Hz]	0.36	0.08	5.59
Q[d]	0.01	0.01	0.23
ϑ[e] [$\times 10^{-3}$]	2.52	2.28	2.39
condition number	3.71	2.69	2.52

[a] For full details see the Supporting Information (Tables SI 8–SI 10). [b] Number of RDCs used. [c] Root mean square deviation. [d] Quality factor as defined by Cornilescu et al.[59] [e] Generalized degree of order: $\vartheta = \sqrt{2/3\left(S_{xx}^{d^2} + S_{yy}^{d^2} + S_{zz}^{d^2}\right)}$.[58]

The local order tensor orientations are depicted by plotting intersections of their eigenvectors with a sphere of radius unity (Figure 5). In addition Monte Carlo simulations were used to gain information about the possible distribution of each principal vector assuming an experimental error of 3 Hz. As is evident in Figure 5, the eigenvectors of the local order tensor of each unit are almost collinear, confirming that **2** shows the same spatial orientation of the fragments in solution as that proposed in structure **A**.[60]

Knowing that the orientation of the fragments in **2** is correctly represented by **A**, we then investigated the flexibility of the cyclohexenyl ring. There are several ways to deal

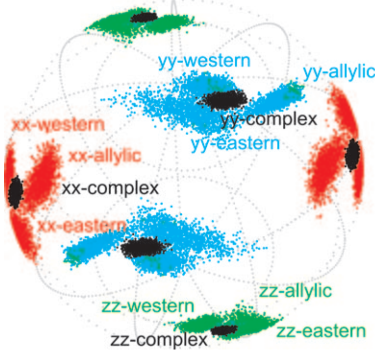

Figure 5. Intersections of the eigenvectors of the local order tensors for **A** with a unit sphere. Note that every component is reflected at the origin of the sphere as a result of insensitivity of the order tensor to axis inversion.

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with flexibility in organic compounds when using (residual) dipolar couplings.[46,57,61] The method we chose here is to superimpose conformer **A** with the allylic ligand in chairlike ($\mathbf{A}^{\text{chair}} = \mathbf{A}$) and boatlike ($\mathbf{A}^{\text{boat}}$) conformations by using Eckart conditions and then performing a population scan in a multiconformer single tensor fit. The best fit corresponds to roughly 57% of $\mathbf{A}^{\text{chair}}$ and 43% of $\mathbf{A}^{\text{boat}}$ (see Figure SI5 and Table SI11 in the Supporting Information). This is consistent with the negligible energy differences between the two conformers, as determined by DFT calculations (Table SI12 in the Supporting Information).[51]

In summary, we have investigated by means of residual dipolar couplings the key intermediate of an enantioselective Pd-catalyzed allylic substitution, the conformation of which could not be determined by conventional NMR methods. Orientation of the sensitive intermediate was possible in high-molecular-weight PBLG. In addition to standard fitting routines, we also used local order tensors to determine the orientation of the fragments with respect to each other. In this way we determined that the solution conformation resembles structure **A**. We were also able to confirm that the cyclohexenyl ligand is flexible with almost equally populated chair- and boatlike conformations.

The determination of the conformation of the intermediate is the first step towards understanding the reactivity and enantioselectivity in this Pd-catalyzed allylic substitution. The structural information obtained in this study will now be used for thorough theoretical investigations towards the reasons for enantioselection.[50]

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