Molecular Mechanics (MM3*) Force Field Parameters for Calculations on Palladium Olefin Complexes with Phosphorus Ligands

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Molecular mechanics parameters have been developed for palladium−olefin complexes with phosphorus ligands, based on a combination of crystal structure and quantum chemical data. The bonding to palladium was described by a valence bond approach, with interactions between the olefin and other ligands modeled by a combination of van der Waals forces and torsional interactions. The accuracy of the derived force field is discussed and tested for a recent application in palladium-assisted allylic alkylation.

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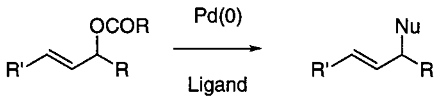
Introduction

The coordination of an olefin to palladium is an important step in many palladium-catalyzed reactions, such as the Heck reaction, the addition of nucleophiles to olefins, and the allylic substitution reaction (Scheme 1).[1]

In the allylic substitution reactions, olefin coordination to palladium(0) is involved both in the initial state of the reaction and in the formation of the substituted olefin product (Figure 1).[2−4] The initially formed complex between palladium(0) and the allylic substrate undergoes an oxidative addition leading to the η^3-allyl palladium(II) complex. Subsequent attack of a nucleophile leads to a new palladium(0)−olefin complex,[3] which regenerates the palladium(0) catalyst by dissociation of the product. The reaction is complicated by dynamic equilibria in the η^3-allyl palladium(II) complex.[2] In addition, the relative rates of the steps in the reaction are strongly influenced by experimental conditions. However, the reaction path depicted in Figure 2 is valid for several cases which have been investigated in some detail. The oxidative addition is rapid and reversible, with the equilibrium lying on the side of the η^3-allyl palladium(II) complex,[4] whereas the final attack of carbon nucleophiles usually is irreversible.[5] It is possible to shift the relative rates of the two steps and thus to make the oxidative addition rate limiting. This can be accomplished either by the use of an intramolecular nucleophile (increasing the rate of the nucleo-

Scheme 1



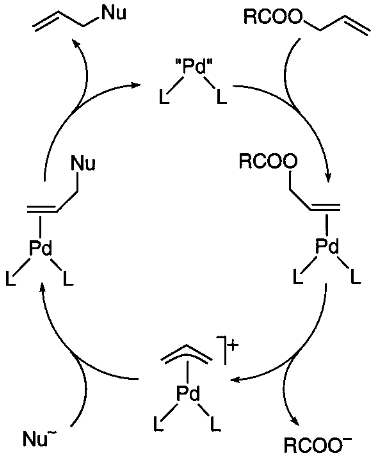


Figure 1. Catalytic cycle for the palladium-assisted allylic alkylation reaction.

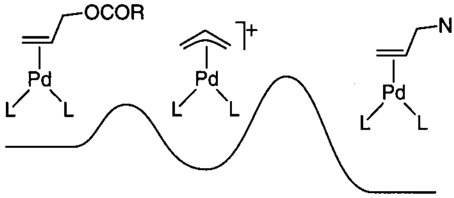


Figure 2. Energy level diagram for the palladium-assisted allylic alkylation reaction.

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philic attack)[6] or by continuous removal of the leaving group (as in the BSA procedure).[7]

Through the use of chiral ligands, the allylic substitution reaction can be made enantioselective, providing an excellent route to the asymmetric formation of new carbon−carbon bonds. If the oxidative addition step is made rate limiting (vide supra), the complex can be made to choose between enantiotopic substrates, leading to either desymmetrization[6] or kinetic resolution.[8] In these cases it should be possible to predict the enantioselectivity from geometries and energies of the isomeric palladium(0) complexes of the allylic substrates. On the other hand, the most common test systems for the palladium-assisted allylic substitution reaction lead to symmetrically 1,3-disubstituted η^3-allyl complexes (e.g., 1,3-diphenyl allyl or cycloalkenyl). In this case, enantioselectivity can only arise from induced regioselectivity in the nucleophilic attack.[9] Selectivity in this step has mainly been predicted from characteristics of the intermediate η^3-allyl complex,[2,10,11] but it has been demonstrated that the relative stability of the product palladium−olefin complex can influence the selectivity strongly.[9,11] Transition states for the nucleophilic addition step have recently been identified using quantum chemical calculations (QC).[12,13] As expected, the transition-state geometries show similarities to both the η^3-allyl−palladium(II) and to the palladium(0)−olefin complex, indicating that a proper description of both types of complexes is needed for a full understanding of the reaction selectivity. The same is true for the oxidative addition step.[13]

It is clear from the above that the coordination of olefins to palladium(0) is of importance in the palladium-assisted allylic substitution reaction. A method for studying these complexes is therefore of great interest. The limited number of X-ray structures reported indicate the instability and the difficulty of obtaining crystals for these complexes. A good alternative is to obtain data from QC calculations. Several recent studies have demonstrated that high-level calculations on palladium complexes of reasonable size are feasible.[12−14] Intermediates and transition states can be identified, and the energy differences between all structures along the reaction coordinate can be determined with good reliability. However, these calculations are still limited to small model complexes. When dealing with large ligand systems, it is not always possible to use a model of the total system. This is especially true when the ligand system forms a chiral pocket that causes the observed enantioselectivity. QC calculations on the whole system would be very time-consuming and, at levels where the calculations could be performed, would not reproduce the critical nonbonded interactions with sufficient accuracy. These systems would be better handled using force field calculations.

Molecular mechanics (MM) for organic compounds is a mature science today.[15,16] Accuracy around 2 kJ/mol for the energy difference between conformers of simple organic compounds was achieved almost two decades ago, and several current force fields can match this performance today.[17] MM calculations are very fast, and conformational searches can easily be performed. In addition, van der Waals forces are better described by empirical force field than by production-level QC calculations.

Application of MM in the field of transition metal chemistry is well established,[18−22] but is still not as generally applicable as for standard organic substrates. Most applications have been based on parameters specifically derived for one particular set of ligands and one or a few metals. A few attempts have been made to broaden the scope to a significant part of the periodic table.[22,23]

A frequently encountered problem when applying MM to metal complexes is how to handle π-bonding.[18,19] Most of the solutions in the literature have been implemented for cyclopentadienyl (Cp) complexes, but the protocols apply similarly to olefin complexes. The simplest approach is to handle all interactions with the π-ligand as nonbonded interactions. When this approach is implemented, the interactions between the metal and the π-atoms are usually described by special parameters defining a deep well.[24] A conceptually very similar model

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is obtained using the POS model,[18,19] the main difference being that the direct interaction is described by a bond function, not a strengthened nonbonded function. A modification of this model is to include a standard angle bending function for small interligand angles.[25] A fundamentally different approach is to bind the ligand to the metal through a "dummy atom" (also called "pseudoatom"), usually defined as the centroid of the π-system.[26−28] In this way, it is possible to specify preferred angles to other ligands, as well as torsional potentials for rotation of the π-ligand around the metal−ligand axis.[26] The latter can be particularly important in late transition metal complexes of olefins, where back-bonding has a strong influence on the preferred geometry.

Some of the available tools[29−31] have been tested for our particular system, but have been found insufficiently accurate for the problems at hand. It is not always obvious how π-coordination should be handled. We have tried several different input methods in the programs available to us. In most cases, the basic trigonal planar coordination of palladium could not be reproduced. Another common error was that the olefin preferred an orientation perpendicular to the coordination plane (a direct result of using uncorrected POS-type models). We therefore decided to develop a new force field for palladium(0)−olefin complexes, to be used in conjunction with the already existing η^3-allyl palladium force field[32] in the study of the palladium-assisted allylic substitution reaction. The final performance is compared to two methods available in the Spartan package.[29]

Computational Details

The parametrization and all calculations using the newly developed parameters were performed using a modified MM3* force field in MacroModel Version 6.5 for Silicon Graphics workstations.[33] Comparative calculations were carried out using the Merck and Sybyl force fields supplied with Spartan SGI Version 5.0.1.[29] The semiempirical calculations were done using the PM3(tm) method in Spartan Version 4.0.3.[29] All QC calculations were performed using the B3LYP[34] method and the LANL2DZ[35] basis set in Gaussian94[36] augmented with one d function (0.37) for the phosphorus atoms and one d function (0.75) for the olefin carbons.

Parametrization

Several available force fields can be used as a basis for implementation of a new parameter set. The optimal choice will depend on, for example, the final use of the force field, the ease of adding new parameters, and the functional form of the force field. We decided to work with MM3* in MacroModel,[33] which has been shown to be one of the most accurate force fields available.[17] Of importance to us was also the possibility of incorporating energy second derivatives in the parametrization (Hessian data).[37] The MM3* force field has a sufficiently advanced functional form to allow meaningful comparisons of vibrational data and therefore permit QC-determined Hessians to be used as reference data. Another advantage with this choice was the compatibility with the earlier developed force field for η^3-allyl palladium complexes.[32]

A dummy-atom approach to ligand binding is not easily implemented in MacroModel, especially in conjunction with parametrization using normal mode data, as the elements corresponding to the dummy atom cannot be projected out of the calculated Hessian.[28] The interactions between olefin and other ligands were therefore implemented as tailored van der Waals interactions using the POS model that has been incorporated into recent versions of MacroModel.[33] The out-of-plane bending and rotational profile were modeled by nonstandard[38] dihedral parameters.

A force field that is to be used in predictions of structure and stability of different conformers has to be parametrized against data of both structure and energy type. Accurately determined X-ray structures are useful reference structural data. However, care has to be taken, since crystal packing forces may cause severe deviations of the geometries, and this should be taken into account. Any accurately known energy difference between isomers is valuable and should be included as reference energy data. QC results are also very important, as they can provide geometrical reference data as well as energy data. Inclusion of energy second derivatives (the Hessian) from the QC calculations adds a high number of data points of high relevance for determination of the force constants. The latter is difficult to achieve using any other type of reference data.

The number of X-ray structures for palladium(0) olefin complexes with phosphorus ligands is very limited. Four suitable X-ray structures[39] (Chart 1) were

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[30] *Cerius2*, SGI version 3.8; Molecular Simulations Inc.: 9685 Scranton Road, San Diego, CA 92121-3752. For the latest version, see: http://www.msi.com.

[31] *PCModel*, version 5.03 for Macintosh; Serena Software: Box 3076, Bloomington, IN 47402-3076. For the latest version, see: http://www.serenasoft.com.

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[38] The dihedral angle was not defined as a bond torsion, but directly using the ligand atoms. Such nonstandard parameters are easily added using the Macromodel substructure recognition facility.

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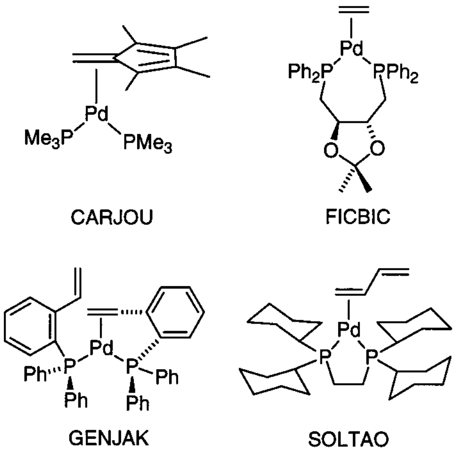
Chart 1. X-ray Structures Included in the Parametrization



found in the Cambridge Crystallographic Data Base and were used as geometrical reference data in the optimization of the parameters. Using all bond lengths, bond angles, and torsions for which a parameter was refined as reference data resulted in 160 data points. No experimental energy data could be found. Thus, we had to rely on QC-calculated reference data to increase the number of data points. Three different model structures (**1**−**3**, Figure 3) were chosen and optimized using "standard" QC methods (B3LYP).

Structure **1** was selected as a simple model of an olefin coordinated to palladium with phosphine ligands. The transition state (**2**) for the olefin rotation of structure **1** was also optimized, to obtain both a strained geometry and the rotation barrier. To permit calculations on allylic acetates and include parameters for these structures, structure **3** was taken as a small symmetrical model compound. Note that the minimum energy structures **1** and **3**, with the olefin in the plane of the ligands, will not be predicted from a simple POS model based solely on steric repulsion. The tailored torsional parameters included in the current force field are critical for the correct representation of the structures.

The optimized geometries, especially the hydrogen positions, from these calculations were used as geometrical reference data (an additional 154 data points). The energy difference between structures **1** and **2** was used as one data point with a high weighting factor. Using the mass-weighted Hessian elements in the parametrization resulted in another 13 221 unique data points. From these calculations 22 calculated ChelpG charges were also used.[40] As for the allyl force field[32a] the charges being reproduced were the group charges for heavy atoms with attached hydrogen atoms.

Based on the selected reference data, a penalty function[41] was defined as a squared sum of weighted deviations of the force field calculated values for all data points. The penalty function was then minimized by standard least-squares methods.[37]

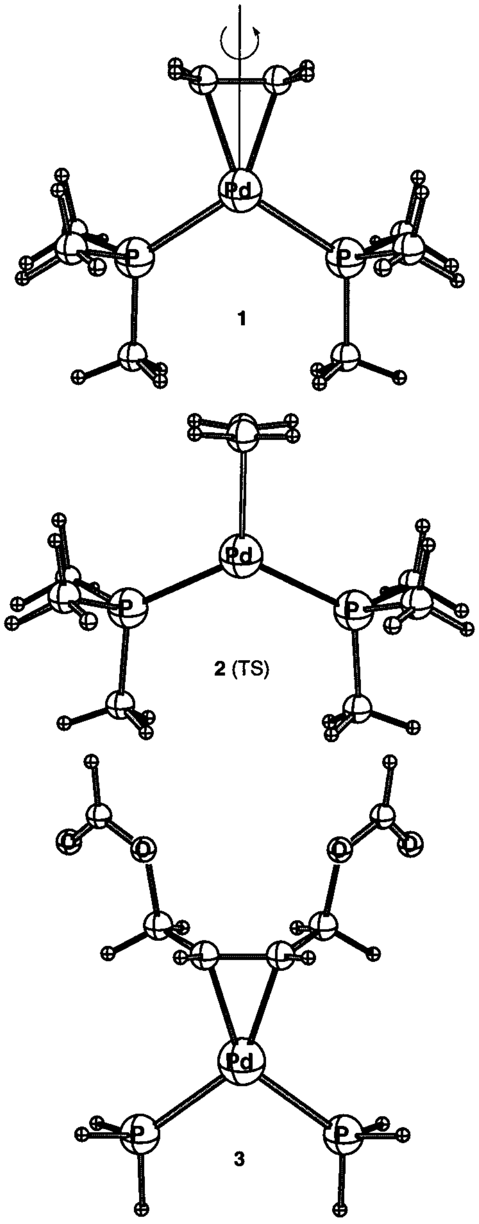


Figure 3. QC reference structures.

An initial estimate of all parameters is required before performing a parametrization. To avoid unnecessary time-consuming optimizations and also the introduction of unreasonable parameter values, these initial guesses have to be chosen carefully. There is also a risk of finding a false minimum of the penalty function, if parameter values too far from their optimal values are used. Geometrical parameters can usually be calculated from available data. Initial values of force constants are more difficult to obtain. Due to the varying functional form of different force fields, force constants are usually not transferable between force fields. The preferred choice would be to use force constants from similar structures in the force field being modified or from other similar force fields.

In the parametrization, the initial geometrical parameters, except for hydrogen, were taken as averages from the X-ray structures. The hydrogen values were

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(41) In previous publications (refs 32, 37, and 43) the term "merit function" was used. However, as an increased value corresponds to a worse force field, "penalty function" is a more appropriate term.

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Table 1. Weight Factors Used in the Parameterization

	X-ray	B3LYP	B3LYP (H)[a]	unit
		Structural Data		
bond length	100	20	100	Å^{-1}
bond angle	2	0.5	2	deg^{-1}
torsion	1	0.3	1	deg^{-1}
		Nonstructural Data		
relative energy			10	kJ^{-1} mol
Hessian element[b]			0.01[c]	kJ^{-1} mol Å^2 amu^{-1}
ChelpG charges			50	au^{-1}

[a] Structural data including at least one hydrogen. [b] Mass-weighted energy second derivative. [c] 0.5 for all atoms in a 1−4 relationship, refs 42 and 43.

Table 2. Optimized Parameters[a]

bond	l_0	k_s
C_c-C_c	1.4103 ± 0.0001	6.5307 ± 0.0001
C_c-Pd	2.1304 ± 0.0001	2.2484 ± 0.0005
$Pd-P$	2.2604 ± 0.0005	1.6395 ± 0.0001
$P-C_{sp3}$	1.8189 ± 0.0088	2.5711 ± 0.1512
C_c-H	1.1119 ± 0.0001	4.3359 ± 0.0001

angle	θ_0	k_b
$C_c-Cc-Pd$	70.2555[b]	0.0000
$Pd-C_c-C_{sp2}$	109.0468 ± 0.0001	1.0838 ± 0.0005
$Pd-C_c-C_{sp3}$	98.6363 ± 3.3167	0.7257 ± 0.3208
$Pd-P-C_{sp2}$	115.2943 ± 0.0005	0.7948 ± 0.0001
$Pd-P-C_{sp3}$	116.4723 ± 0.0333	0.6159 ± 0.0432
C_c-C_c-H	120.7026 ± 0.0001	0.479 ± 0.0005
$Pd-C_c-H$	124.44 ± 0.0001	0.0733 ± 0.0005

atom 1	atom 2	μ[c]	charge flux[d]
C_c	Pd	−0.0344 ± 0.0001	−0.003
Pd	P	−3.8652 ± 0.0001	−0.356
P	C_{sp3}	0.2042 ± 0.0053	0.025
C_c	H	−0.2801 ± 0.0001	−0.052

vdW parameters	R	ϵ
Pd	2.3701 ± 0.0005	0.414 ± 0.0001
$C_c \cdots P$[e]	4.0875 ± 0.0001	0.3351 ± 0.0005
$P \cdots P$[e]	5.2037 ± 0.0001	0.1465 ± 0.0001

torsion	v_2	v_3
$Pd-C_c-C_c \cdots P$[f]	13.211 ± 0.0001	
$Pd-C_c-C_{sp2}-C_{sp2}$		−1.1022 ± 0.0001
$Pd-C_c-C_{sp2}-O_{sp2}$		−1.1022[b]
$Pd-C_c-C_{sp3}-O$		0.3356 ± 0.5227
$P-Pd-P-C_{sp2}$	−0.0498 ± 0.0005	−1.4845 ± 0.0001
$P-Pd-P-C_{sp3}$		−0.0355 ± 0.0051
$C_c-P-P-Pd$	2.5030 ± 0.0005	
$H-C_c-C_c-H$	5.6643 ± 0.0005	0.7371 ± 0.0001
$H-C_c-C_c-C_{sp2}$	0.0591 ± 0.0005	−1.4523 ± 0.0001
$Pd-C_c-C_{sp2}$		−1.8121 ± 0.632
$Pd-C_c-C_{sp3}-H$		−0.0808 ± 0.2484
$P-Pd-P-H$		−0.0771 ± 0.0207

[a] Units: l_0 [Å], k_s [mdyn/ang], θ_0 [deg], k_b [mdyn/rad^2], v [kcal/mol], μ [debye], R [Å], ϵ [kcal/mol]. Note that the ranges supplied for each parameter do not reflect the absolute accuracy, but rather are a statistical measure of what variation could be allowed without significantly worsening the fit, under the assumption that the source data are exact. [b] Parameter not refined. [c] Dipole parameter. Only used internally to calculate charge flux. [d] Calculated from dipole. The charge is added to atom 1 and subtracted from atom 2. [e] Used when bonded to the same Pd. [f] Phosphorus is bonded to Pd, not C. The parameter is not required by the force field, but was added to enable fitting of the rotation barrier.

taken from the QC calculations. The corresponding force constants were taken from similar structures in the MM3* force field[33] or in the related allyl force field.[32] The charge flux parameters were modified manually to reproduce approximately the calculated ChelpG charges. The initial palladium parameters were taken from the allyl force field and modified accordingly.

For the X-ray structures the recommended weight factors[37] were used without modification. The same weight factors were used for the QC-determined hydrogen positions, while other geometrical data from the same calculations were given lower weight factors. The calculated energy difference was also given a slightly lower weight factor than that recommended for energy data. Hessian elements connecting atoms in a 1−4 relationship are important for a unique determination of torsional constants and were therefore given a high weight factor.[42] All weight factors used in the parametrization are given in Table 1.

The parameters were optimized using the parametrization procedure described by Norrby and Liljefors.[37] The penalty function (the sum of squares of weighted deviations from the reference values) was minimized by varying the parameters using Simplex and Newton−Raphson optimization techniques alternatingly.[32a,37,43] The parameter refinement was continued until there was no further improvement of the penalty function. The first and second derivatives of the penalty function with respect to each parameter were then checked to make sure that the second derivative is always positive and large with respect to the first derivative.[43] Full convergence was achieved, allowing an estimate of the confidence interval of each parameter. This was defined as the range within which a parameter can be varied without increasing the penalty function significantly. In this case, we chose to define the limit arbitrarily as 0.1% of the total penalty function.[43] Note that the absolute accuracy is lower, as the source data are not exact. The ranges are shown together with the parameters in Table 2.

Results

The optimized parameters are given in Table 2. Figure 4 gives an overlay of the X-ray structures used in the parametrization and the corresponding structures after minimization using the new force field. Similar comparisons of the QC structures **1−3** with both force field and PM3(tm) results are shown in Figure 5. In all overlays, only palladium and the atoms directly attached to palladium are superimposed. The rms values for these overlays are given in Table 3.

The rotation barrier calculated by the force field was 53 kJ/mol, to be compared with 54 kJ/mol from the QC calculation. This good correspondence was expected, since the barrier was used with a comparatively high weight factor in the refinement.

A few additional X-ray structures[44] were used for validation (Chart 2). These were not included in the parameter refinement. In the case of HADSIO, the structure was excluded from the refinement cycle due to the unusual electronic properties of the double bond and also because of time considerations due to the large C_{60} unit. All the other structures in Chart 2 have a carbonyl group conjugated with the double bond. In

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(42) Maple, J. R.; Hwang, M.-J.; Stockfisch, T. P.; Dinur, U.; Waldman, M.; Ewig, C. S.; Hagler, A. T. *J. Comput. Chem.* **1994**, *15*, 162.

(43) Brandt, P.; Norrby, T.; Åkermark, B.; Norrby, P.-O. *Inorg. Chem.* **1998**, *37*, 4120.

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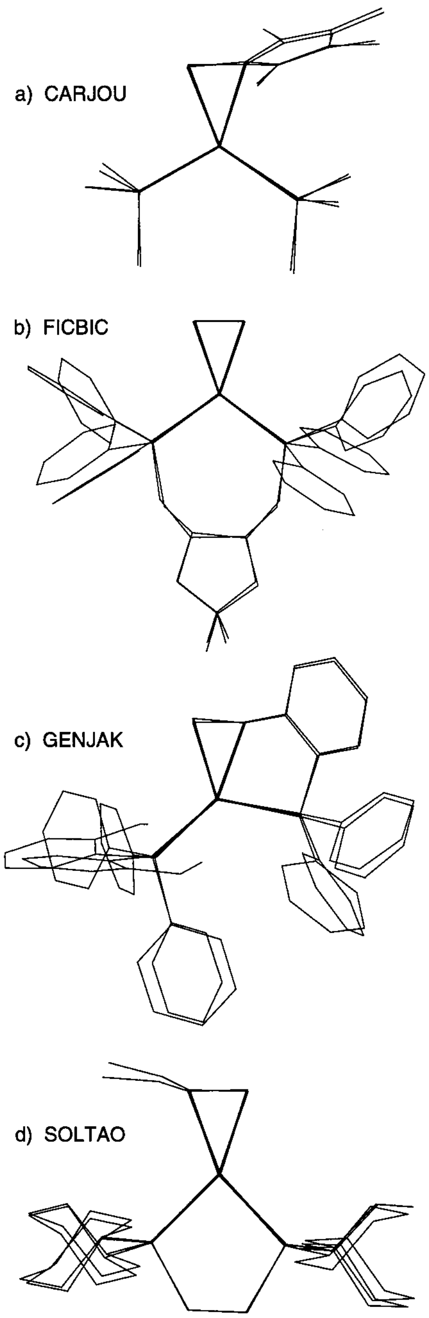

Figure 4. Overlays of palladium and directly attached atoms in X-ray and MM3* minimized structures.

general, force field calculations are not expected to reproduce structural changes based on purely electronic differences, so the results for the validation set (Chart 2) are expected to be less accurate than for the training set. Figure 6 shows the superpositions of palladium and directly attached atoms in the X-ray and the minimized structure. The corresponding rms values are given in Table 3.

All structures were also minimized using the PM3(tm) semiempirical method and the Sybyl and Merck force fields as implemented in Spartan.[29] The rms values for superposition of these structures and the corresponding X-ray structure are included in Table 3. A few selected structures are shown in Figures 7–9, and some important geometrical parameters for the structures are listed in Tables 4 and 5.

For validation of the force field in rationalization of enantioselectivity, calculations were also performed on palladium complexes of ligand **4** with olefins **5** and **6**, from a recent study of kinetic resolution.[8] The conformational space of the diastereomeric complexes was searched using the Low-Mode search option in MacroModel.[45] As the acetate group must be expelled from a conformation where the acetate is anti to palladium, only such conformations were considered. For both substrates, the best (*S*)-conformer found was lower in energy than any (*R*)-conformer, by 1 kJ/mol for **5** and 2 kJ/mol for **6**.

Discussion

A fair amount of reference data points were used in the parametrization despite the limited number of reference structures. With a total of 13 558 reference data points the 46 reported parameters should be fairly well determined. The force field is fully converged, so that no single parameter can be varied to give a better penalty function. Inclusion of additional X-ray structures or experimentally determined energy differences would have been beneficial, but is clearly not needed to obtain a reliable force field. The only energy difference included is reproduced within 1 kJ/mol. As can be seen from the overlays (Figures 4–6) and from the rms values in Table 3, the agreement with structural reference data is good.

Of the X-ray structures included in the parametrization, only one structure, GENJAK, gives a high rms value (Figure 7). This structure has an internal ligand, where the olefin is covalently bonded to another ligand. From Table 4 it can be seen that the largest deviation is attributed to the P–Pd–P bond angle, 9°. The interaction between ligands in the POS model is obviously not strong enough to counter the strong strain introduced by the covalent linker. Other structural features (in particular bond lengths) are still better represented by the current force field than by other methods represented in Table 4, but it is clear that caution must be exercised when using calculated structures for highly strained systems. The performance could probably be improved by using a regular MM bend function for the P–Pd–P angle, but it is not obvious how this could be combined with a POS model for the olefin within the MacroModel program.

The QC-calculated data are fairly well reproduced. In these complexes the force field always give shorter palladium bond distances when compared to the QC-calculated structures, but most values are fairly close. Since bond lengths agree well in crystal structures and force field calculations, the deviation most probably represents a small systematic error in our chosen QC method. One structure is described less well by the force field, the high-energy tetrahedral complex **2**. As can be seen in Table 5, the force field gives geometrical

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(44) HADSIO: Bashilov, V. V.; Petrovskii, P. V.; Sokolov, V. I.; Lindeman, S. V.; Guzey, I. A.; Struchkov, Yu. T. *Organometallics* **1993**, *12*, 991. WEDFOA: Herrmann, W. A.; Thiel, W. R.; Brossmer, C.; Ofele, K.; Priermeier, T.; Scherer, W. *J. Organomet. Chem.* **1993**, *461*, 51. YIZHIY: Goddard, R.; Hopp, G.; Jolly, P. W.; Kruger, C.; Mynott, R.; Wirtz, C. *J. Organomet. Chem.* **1995**, *486*, 163. YIZHOE: Fawcett, J.; Kemmitt, R. D. W.; Russell, D. R.; Serindag, O. *J. Organomet. Chem.* **1995**, *486*, 171.

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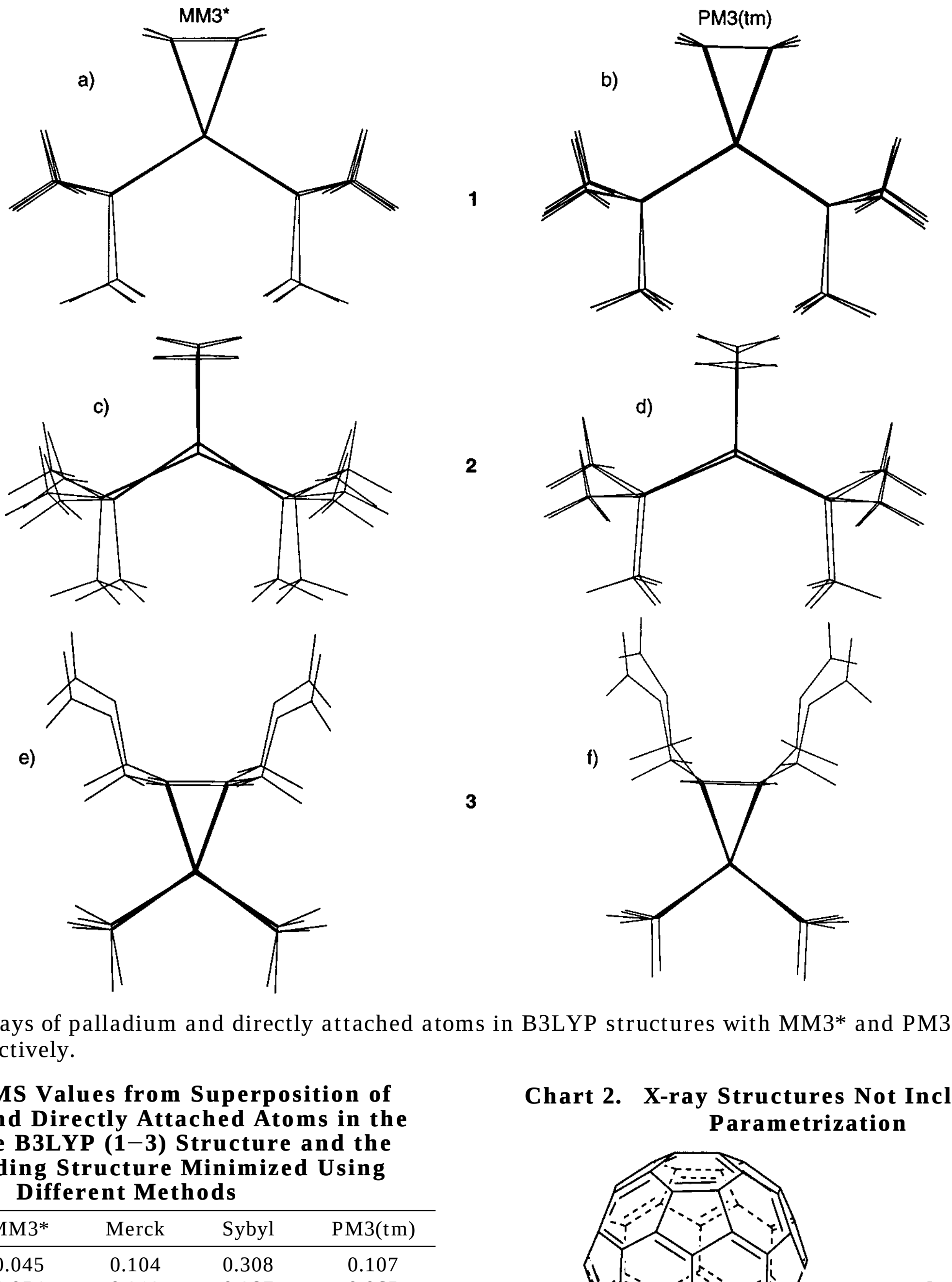
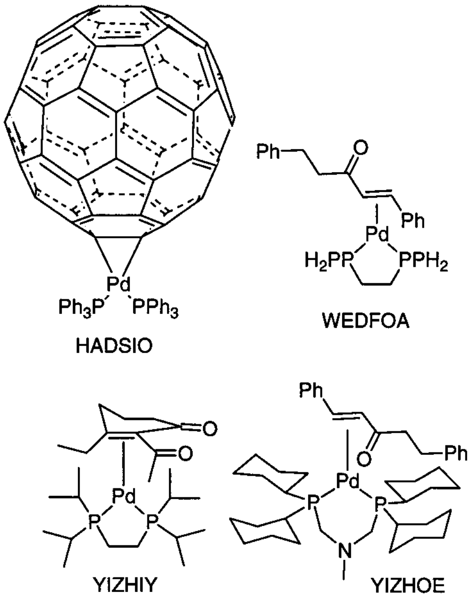


Figure 5. Overlays of palladium and directly attached atoms in B3LYP structures with MM3* and PM3(tm) minimized structures, respectively.

Table 3. RMS Values from Superposition of Palladium and Directly Attached Atoms in the X-ray or the B3LYP (1–3) Structure and the Corresponding Structure Minimized Using Different Methods

structure	MM3*	Merck	Sybyl	PM3(tm)
CARJOU	0.045	0.104	0.308	0.107
FICBIC	0.054	0.212	0.287	0.065
GENJAK	0.078	0.234	0.184	0.093
SOLTAO	0.039	0.286	0.235	0.063
1	0.064	0.075	0.077	0.130
2	0.211	0.145	0.195	0.152
3	0.076	0.123	0.136	0.125
	Not in Parametrization			
HADSIO	0.117		0.289	
WEDFOA	0.055	0.190	0.244	0.101
YIZHIY	0.128	0.175	0.287	0.059
YIZHOE	0.078	0.143	0.224	0.074

Chart 2. X-ray Structures Not Included in the Parametrization



parameters of **2** that are close to the parameters of **1**, while the QC calculation gives considerably different values. The differences between the structures are in part due to electronic interactions between the palladium and the ligands (different orbitals used for bonding between palladium and the olefin) and can therefore not be expected to be fully reproduced by the force field. In the transition state structure (**2**) the back-bonding from palladium to olefin is strongly reduced, with the effect that the olefin bond is shortened and the distance to palladium is increased. To compensate, the Pd–P bonds are strengthened and the P–Pd–P angle

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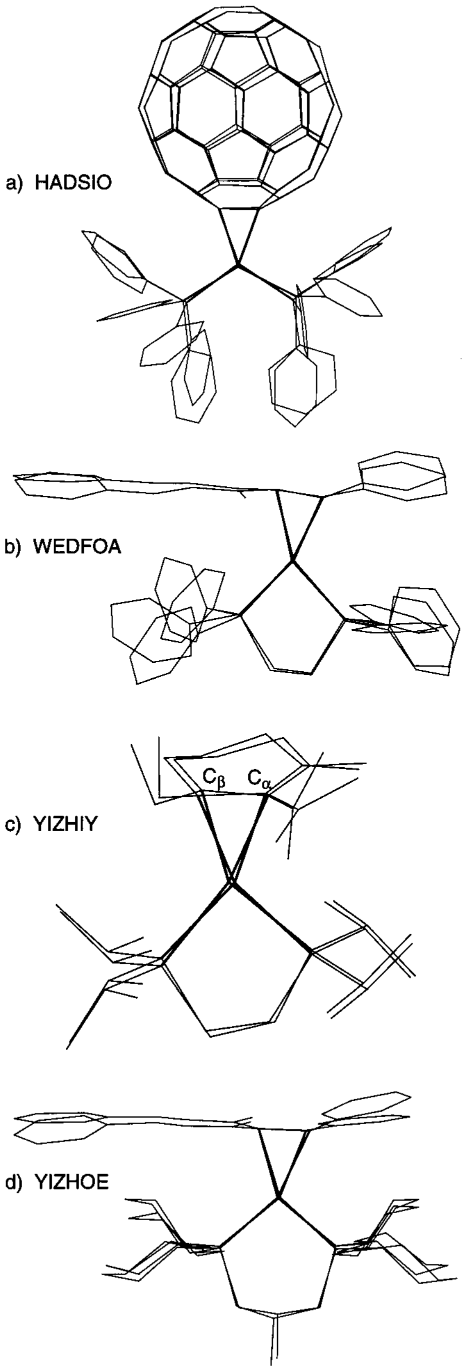
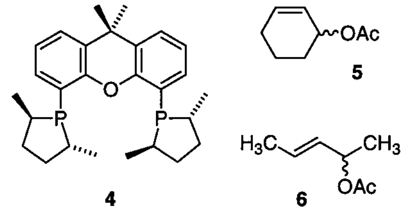


Figure 6. Overlays of palladium and directly attached atoms in X-ray and MM3* minimized structures.

Chart 3. Structures Used in Validation of the Force Field for Kinetic Resolution



is increased. Overall, the electron density on palladium is higher in **2** than in **1**, as evidenced both by Mulliken population analysis and by the ChelpG charges.

The agreement with X-ray data not included in the parametrization is almost as good as for the training set, despite the electronic differences. The YIZHIY structure gives the highest rms value. The largest differences are in the P−Pd bond lengths (Table 4). In the X-ray structure the P−Pd bond that is trans to the two carbonyls is 0.044 Å shorter than the other P−Pd bond. The carbonyl substituents drain the electrons of the olefin, and the trans phosphine compensates by increasing the donation resulting in a shorter P−Pd bond length. The force field does not include any protocol for differentiating between electronically different olefin carbons and can therefore not reproduce the observed

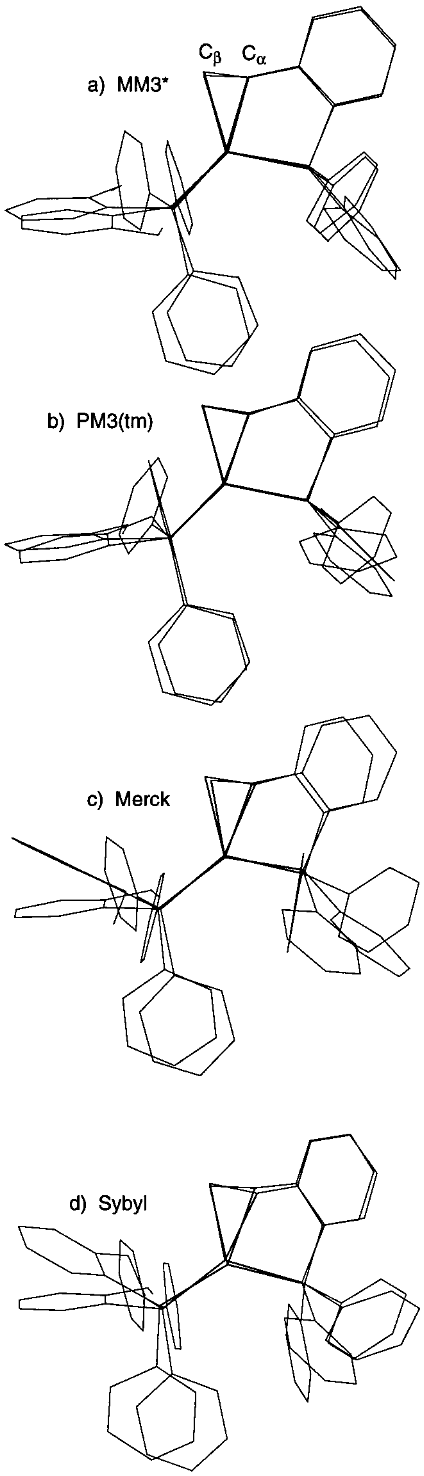


Figure 7. Overlays of GENJAK and structures minimized using different methods.

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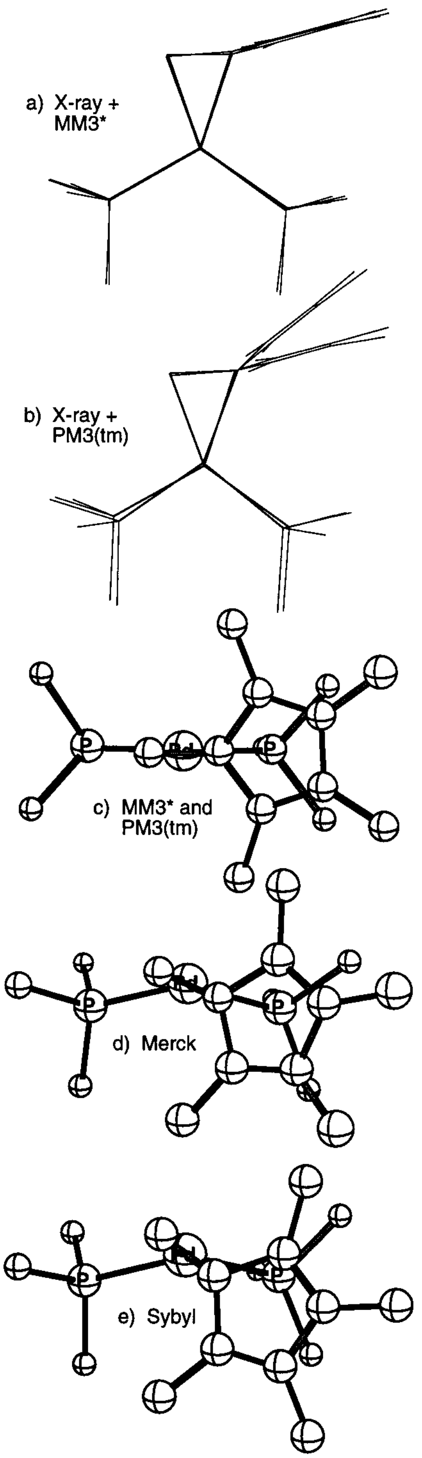

Figure 8. CARJOU and structures minimized using different methods: (a and b) side views; (c–e) top views.

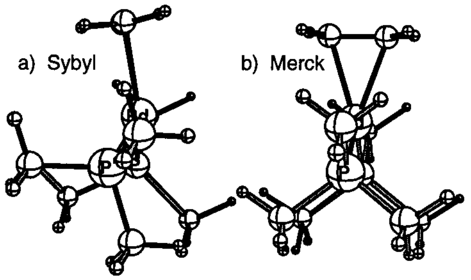

Figure 9. Structure **1** minimized using the Sybyl and Merck force fields.

Table 4. Geometrical Parameters of the GENJAK and YIZHIY Structures

	X-ray	MM3*	PM3	Merck	Sybyl
		GENJAK[a]			
C_α–Pd	2.140	2.188	2.108	2.205	2.323
C_β–Pd	2.213	2.147	2.145	2.137	2.304
C_α–C_β	1.387	1.412	1.475	1.341	1.348
Pd–P	2.305	2.274	2.298	2.335	2.402
Pd–P	2.303	2.304	2.273	2.368	2.418
P–Pd–P	121.4	130.2	118.3	121.2	120.1
C_β–C_α–C	126.0	127.4	124.9	123.3	123.2
		YIZHIY			
C_α–Pd	2.163	2.193	2.143	2.252	2.443
C_β–Pd	2.140	2.162	2.156	2.294	2.433
C_α–C_β	1.455	1.428	1.518	1.359	1.345
Pd–P	2.327	2.355	2.282	2.346	2.393
Pd–P	2.283	2.329	2.274	2.342	2.391
P–Pd–P	88.6	87.1	86.1	93.7	94.9

[a] See olefin carbon notations of Figures 6 and 7.

Table 5. Geometrical Parameters of QC-Generated Structures

	QC	MM3*	PM3	Merck	Sybyl
		Structure **1**[a]			
C_c–Pd	2.188	2.144	2.093	2.141	2.281
C_c–C_c	1.411	1.412	1.489	1.337	1.346
Pd–P	2.389	2.302	2.265	2.325	2.401
P–Pd–P	115.1	116.4	107.4	119.9	122.5
		Structure **2**			
C_c–Pd	2.452	2.145	2.181	2.133	2.275
C_c–C_c	1.363	1.413	1.411	1.337	1.347
Pd–P	2.385	2.291	2.291	2.320	2.399
P–Pd–P	130.0	111.4	124.4	119.6	120.6

[a] C_c = Coordinated olefin carbon.

effect. In the structure calculated by the force field, the rotation of the olefin moiety out of the P–Pd–P plane is also too high by ca. 5° when compared to the X-ray.

In general, the performance of the PM3(tm) method is slightly worse than the force field. Only for GENJAK does the PM3(tm) method give a lower deviation from the experimental structure (Figure 7, Table 3). It is surprising that the semiempirical method does not give a better result for transition state **2**, when compared to the force field. The PM3(tm) method does give a larger P–Pd–P bond angle, but does not reproduce the olefin bond distances. The energy difference between the two structures calculated using this method is 165 kJ/mol, which is more than 3 times higher than the QC-determined value. For the structures not included in the parametrization the PM3(tm) method and the force field give comparable results. As expected, when electronic effects are involved, the PM3(tm) does reproduce the YIZHIY structure better.

Apart from being more time-consuming, the PM3(tm) method also exaggerates the bending of the olefin substituents out of the olefin plane. This is not reflected to any appreciable extent in the rms values, since only the atoms directly attached to palladium are superimposed. Thus, the olefin carbons and no substituents are included. However, the bending of the substituent may displace the olefin carbon somewhat, and this will give an increase in the rms value. The deviation is very obvious in the CARJOU structure (Figure 8b).

As can be seen in Table 3, the Sybyl and the Merck force fields always give inferior results when compared

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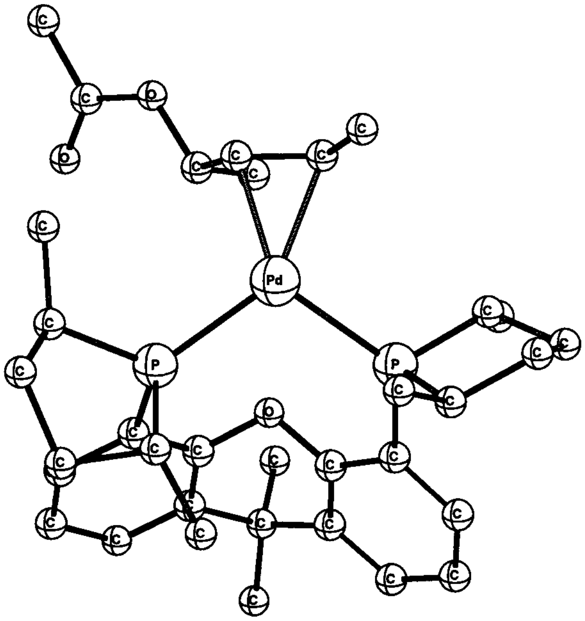

Figure 10. Best palladium complex of ligand **4** and olefin (*S*)-**6**.

to the current force field. It must be kept in mind that Sybyl and Merck are general force fields and do not contain specific palladium olefin parameters. Despite the fact that Spartan allows specification of a trigonal planar palladium, the planarity is not kept upon minimization (Figure 8). For the C_{2v}-symmetric QC structures **1** and **2**, the planarity is of course preserved as long as the symmetry is retained, yielding the deviations reported in Table 5. Minimizing without symmetry constraints instead yields the structures shown in Figure 9.

From these results it is clear that specific palladium olefin parameters are necessary to make any high-quality predictions from molecular mechanics calculations. The current force field is best suited for calculations on complexes where electronic effects are minimized, such as complexes of symmetric olefins where selectivity is induced through steric interactions.

The force field was developed to study the palladium-assisted allylic substitution reaction. Several of the successful ligands used in this reaction are C_2-symmetric and induce enantioselectivity through a chiral pocket.[2a] These ligands are therefore well suited for a molecular mechanics study. To calculate reaction selectivities, it would be preferable to study the isomeric transition states leading to the different products. However, it has been demonstrated that the product distribution in nucleophilic addition can be predicted with high accuracy from the ground-state structures of palladium allyl complexes.[11] It was therefore hoped that the reverse reaction, ionization of allylic acetates, also is amenable to prediction from the reactant ground state, the complex between palladium(0) and allylic acetate. Predictions from such calculations should be treated cautiously. The main assumption is that interactions that develop between the ground state to the transition state have equal influence for the diastereomeric complexes. Work is in progress to allow direct evaluation of transition-state interaction for this reaction,[13,46] but for the time being, we have to make use of semiquantitative methods of the type used earlier[11] and exemplified below.

In a recent publication, the reaction of racemic allylic acetates **5** and **6** with a palladium complex of ligand **4** was studied.[8] From the relative rates reported for reaction of the enantiomers of **5** and **6** in the presence of **4** ($k_S/k_R = 2-8$), it is possible to estimate the difference in energy of activation to 2−5 kJ/mol, with the (*S*)-enantiomer being most reactive for both substrates. Assuming that the reactivity of appropriately positioned allylic acetates are similar, this energy difference should correspond to the energy difference between the best conformations of the diastereomeric complexes. The conformational search correctly identified the (*S*)-enantiomer as having the lowest energy in both cases. For **5**, the best (*R*)-conformation was 1 kJ/mol higher in energy; for **6**, the difference was 2 kJ/mol. Considering the approximations that have been made (neglect of entropic and solvation contributions) and the expected uncertainty in any force field calculation,[17] the close correspondence between calculated and experimental results is gratifying.

Conclusion

The force field reported here can be used to determine structures of palladium(0)−olefin complexes with acceptable accuracy. In many cases, these complexes are too unstable to study experimentally. It has been shown that the force field can yield useful predictions in the palladium-assisted allylic substitution reaction. In conjunction with the recently developed η^3-allyl palladium force field,[32a] the olefin force field can be used to study the entire reaction path. Using the Jensen method,[46] these two force fields can also be used to get an estimate of the transition-state structure.

Only parameters for phosphine ligands were included in this force field. However, the recently developed parametrization routine[37] utilized herein can be used to add parameters for other ligand types as required. Another possible extension would be to allow calculations on palladium(II) complexes to study, for example, the Heck reaction and the nucleophilic attack on coordinated olefins.

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Supporting Information Available: The new force field in MacroModel input format. This material is available free of charge via the Internet at http://pubs.acs.org.

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[46] Jensen, F. *J. Comput. Chem.* **1994**, *15*, 1199.