New Molecular Mechanics (MM3*) Force Field Parameters for Calculations on (η^3-Allyl)palladium Complexes with Nitrogen and Phosphorus Ligands

Helena Hagelin,[†] Björn Åkermark,[†] and Per-Ola Norrby*,[‡]

Department of Chemistry, Organic Chemistry, Royal Institute of Technology,
S-10044 Stockholm, Sweden, and Department of Medicinal Chemistry, Royal Danish
School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark

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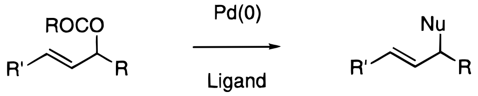
A force field for (η^3-allyl)palladium complexes with phosphorus and/or nitrogen ligands has been developed, based upon both X-ray and quantum chemical reference data. The quality of the force field in structure prediction is checked by comparison to X-ray structures, including several not used in the parametrization. The force field is also compared to alternative computational methods for structure prediction, including earlier force fields and two quantum chemical methods (PM3(tm) and B3LYP/LANL2DZ).

Introduction

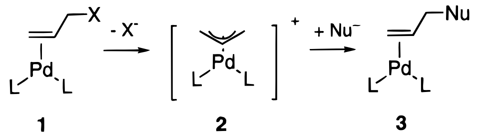
Palladium is one of the most widely used transition metals in catalytic reactions.[1] One synthetically very useful reaction is the palladium-assisted allylic alkylation reaction[2] (Scheme 1). It is well-known that the reaction proceeds via a (η^3-allyl)palladium complex (**2**, Scheme 2).

This intermediate is in several cases stable enough for X-ray crystallographic determination, and a number of structures have been reported.[3] Through the use of chiral ligands this reaction can be made enantioselective and thus offers an exceptional route for the asymmetric formation of new carbon−carbon bonds.[4] Several successful systems containing C_2 symmetric phosphine[5] or nitrogen ligands[6] have been reported, as well as nonsymmetric ligands containing phosphine and/or nitrogen.[7] Even though the intermediate has been identified and thus the reaction path is fairly well-known, it is not always easy to make predictions about the regio- and stereochemical outcome of the reaction. Several factors such as electronic influence from ligands or allyl substituents, steric interactions, and rapid isomerization of the intermediate may influence the outcome of the reaction and must be taken into account. It is clear from the catalytic cycle (Figure 1) that the allyl intermediate plays a central role in the overall reaction. Depending on substrate and reaction conditions, different steps in this cycle can dictate the stereochemistry (Figure 2).[4] Irrespective of whether the selectivity is determined in

Scheme 1



Scheme 2



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* Corresponding author. E-mail: peo@compchem.dfh.dk.

[†] Royal Institute of Technology.

[‡] Royal Danish School of Pharmacy.

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10.1021/om990153z CCC: $18.00

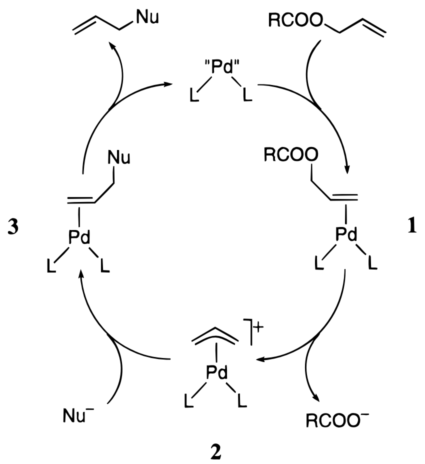

Figure 1. Catalytic cycle for the palladium-assisted allylic alkylation reaction.

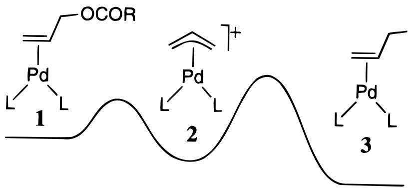

Figure 2. Energy level diagram for the palladium-assisted allylic alkylation reaction.

the ionization or nucleophilic addition step, it is expected that much information about selectivity-determining interactions can be gained from the η^3-allyl intermediate. The barriers in either step should be correlated both with the energy and with structural features of the η^3-allyl complex.[8]

Using C_2 symmetric ligands, the electronic difference between the terminal allylic carbons is eliminated. Steric interactions through a chiral pocket are, therefore, the main contributing factors to the observed selectivity. Small structural changes in these ligands can have a large influence on the overall geometry and thus on the chiral pocket. The resulting effect on the selectivity can be difficult to predict. Supposing that the η^3-allyl intermediate is stable enough, the geometry can be obtained from X-ray crystallography. This approach can give valuable information about possible refinement of the ligand structure, but does have several drawbacks. First, the complex must be synthesized before the study can be initiated, and it may not be possible to get the required material into crystalline form. Second, only the conformation that is most stable in the crystal is observed. This is not necessarily the most important form in the catalytic cycle. However, NMR studies of the solution structure are usually complementary in that alternative forms of the intermediate, their relative populations, and possibly their interconversion rates can be studied.[9] Still, a computational approach could be very valuable, in that the entire conformational space of a complex can be investigated prior to actual synthesis of the ligand. Quantum chemical (QC) calculations are valuable tools in analyzing chemical reactions, and the transition state of the palladium-assisted allylic nucleophilic substitution has in fact been identified recently.[10,11] The disadvantage of these calculations is that they require large computational resources and are limited to fairly small model systems. Many systems would therefore be better suited for a molecular mechanics approach. In fact, molecular mechanics calculations on the η^3-allyl palladium intermediate combined with QSAR methods have been used successfully in the prediction of the regio- and stereochemical outcome of the reaction.[8,12] However, the force field[13] used in these calculations is limited to nitrogen ligands and is quite unwieldy by current standards. Since several of the successful ligands are based at least partly on phosphorus, we decided to broaden the scope and the utility of the method by development of a more up to date and generally applicable force field.

Parametrization

The first and most basic step in the development of a force field for a new functional group is to decide what bonding model to use. This question is often trivial, but for organometallic complexes complications arise.[14] In the previously developed palladium parameters[13] for the Allinger MM2 force field,[15] the underlying program imposed severe restrictions on the model, in that there was no mechanism for differentiating between substituent positions in systems with low symmetry (e.g., square planar complexes). This, together with the fairly rigid functional form for angle bending, necessitated the use of so-called *dummy atoms*. It should be noted that the utilization of dummy atoms in no way detracted from the accuracy of the force field, but it did add a complicating factor, particularly for inexperienced users. Also, the use of dummy atoms introduces additional complications in the calculation of vibrational spectra.[14] To alleviate these complications, we decided to implement a valence bond approach in the MacroModel program,[16] and in particular the MM3* force field. The three allyl carbons and the two ligands were bound to palladium by single bonds. On the basis of the behavior of allyl substituents in our original force field,[13] and to facilitate handling in the graphical interface, all allyl carbons were defined as sp^3 type, with connecting single bonds (the exact connectivity is defined in the MacroModel substructures in the Supporting Information).

The use of MM3* in lieu of MM2* is mainly motivated by the fact that we wanted to include quantum chemically calculated energy derivatives in the parametrization. At the time this project was started, MM3* was the only force field within MacroModel with a sufficiently complex functional form to allow meaningful comparisons of properties dependent on energy second derivatives (the Hessian),[17] which is a necessary

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requirement for this type of parametrization. The MM3* force field has recently been shown to be among the most accurate force fields currently available for energy predictions in organic systems.[18] The MacroModel force field implementation also allows inclusion of low symmetry centers, that is, a differentiation of cis and trans parameters, a necessary requirement for our choice of bond model.

The MM3* force field, which is based on the MM3(91) parameter set, does not include high-quality parameters for the oxazoline moiety. As several of the most successful ligands are based on oxazolines,[7e,f,k,l] we added and refined the required parameters.

The actual parameter refinement is based on a merit function, which is defined as a sum of squares of weighted deviations between calculated and reference data points.[19] The merit function is then minimized by variation of the parameters, using standard Simplex and least-squares methods (vide infra).

Reference Data. To achieve a well-balanced force field, it is necessary to parametrize against both structure and energy reference data. Ideally, structural reference data should be from gas-phase determinations, but this is obviously not possible for most organometallic complexes. X-ray crystal structures may be used in lieu of gas-phase data, with some added precautions. It can be assumed that errors due to crystal packing forces will cancel if (a) a sufficient number of structures are included so that the mean errors tend toward zero; (b) long-distance comparisons are avoided (i.e., structure superposition should not be used as a measure of accuracy, but bonds and angles may be compared); and (c) torsions are given a low weight, since they are generally soft compared to bonds and angles. Parameters involving hydrogens, and torsional parameters corresponding to soft modes, should be determined from other sources. In the current study, we have utilized source data from 25 X-ray crystal structures of 22 different compounds (Chart 1).[20] To account for the variations in the quality of the X-ray structures, it was decided to modify the weight factors described by Norrby and Liljefors[19] accordingly. Structures with low *R*-values were given higher weight factors than structures with higher *R*-values (see Table 1). The X-ray structures were also studied to ensure that the reported allyl geometry was not the result of cocrystallization of rotameric forms. A few suspected errors of this type were found, and these X-ray structures were then given lower weight factors than the corresponding *R*-value otherwise would have indicated (Table 1).

Table 1. Geometrical Weight Factors Used in the Parametrization

type of input	*R*-value	bond length [Å^{-1}]	angle [deg^{-1}]	dihedral [deg^{-1}]
X-ray	0.010−0.020	200	5	2
X-ray	0.020−0.035	150	3	1.5
X-ray	0.035−0.050	100	2	1
X-ray	$\sim$0.05	60	1.5	0.8
X-ray	0.050−0.080	30	0.8	0.4
B3LYP		50	1	0.5

Reliable reference data can be obtained from quantum chemical calculations. There are many types of data from these calculations that can be used as reference data. Geometry optimizations using the B3LYP hybride functional[21] were performed on eight model compounds using the LANL2DZ basis set[22] for all Pd-containing structures (**4**−**8**, Chart 2) and the 6-31G* basis set for the oxazoline structures (**9**−**11**, Chart 2). All quantum chemical calculations were performed in Gaussian94.[23] The optimized geometries were used as reference structural data in the parametrization. Most importantly, the structural data for the hydrogen positions were taken from these calculations (parameters involving hydrogen were ignored in the X-ray reference data). Slightly lower weight factors than those recommended for experimental structures[19] were used for the QC reference data. The mass-weighted Hessian elements were also calculated numerically and used as reference data in the parametrization, resulting in a large number of data points. The latter are mainly important for an accurate refinement of the force constants.

The "bond dipole" parameter in MacroModel is in reality a charge flux parameter. Adjusting this parameter will *only* have the effect of transferring point charge between connected atoms. In previous parametrizations,[24] we have simply adjusted the "dipole" parameters to reproduce ChelpG charges[25] as closely as possible and then kept them constant in the actual parameter refinement. C−H bond dipoles were kept at the original MM3 values. In the current study, we have instead refined the "dipoles" together with other parameters, using atomic ChelpG charges as reference data.[26] This approach (which corresponds to a harmonic tethering to the QC-derived charges) will automatically allow small variations of the charges in the parametrization if a substantial improvement in the force field accuracy can be obtained.

Three energy ratios for syn-anti equilibria (**12**−**14**, Chart 3) determined by NMR[27] were also used in the parametriza-

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(17) A reliable description of the local hypersurface around a potential energy minimum, and through this a good description of the molecular vibrations, requires a force field with a minimum number of off-diagonal terms. For a description of this aspect of MM3, see: Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8566.

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(20) The X-ray structures were taken from the Cambridge Crystallographic Database. Original Publications as follows: ALPQMP: Deeming, A. J.; Rothwell, I. P.; Hursthouse, M. B.; Malik, K. M. A. *J. Chem. Soc., Dalton Trans.* **1979**, 1899. CEKKOS: Godleski, S. A.; Gundlach, K. B.; Ho, H. Y.; Keinan, E.; Frolow, F. *Organometallics* **1984**, *3*, 21. CUYYAW: Farrar, D. H.; Payne, N. C. *J. Am. Chem. Soc.* **1985**, *107*, 2054. FUHMOK: Grant, D. P.; Murrall, N. W.; Welch, A. J. *J. Organomet. Chem.* **1987**, *333*, 403. GAFBAQ: Murrall, N. W.; Welch, A. J. *J. Organomet. Chem.* **1986**, *301*, 109. GEFHOO: Gozum, J. E.; Pollina, D. M.; Jensen, J. A.; Girolami, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 2688. HAJKAE: De Munno, G.; Bruno, G.; Rotondo, Giordano, G.; Schiavo, S. L.; Piraino, P.; Tresoldi, G. *Inorg. Chim. Acta* **1993**, *208*, 67. JERGES: Albinati, A.; Ammann, C.; Pregosin, P. S.; Ruegger, H. *Organometallics* **1990**, *9*, 1826. JOLZIT: Ozawa, F.; Son, T.; Ebina, S.; Osakada, K.; Yamamoto, A. *Organometallics* **1992**, *11*, 171. JOZTAT: Ammann, C. J.; Pregosin, P. S.; Ruegger, H.; Albinati, A.; Lianza, F.; Kunz, R. W. *J. Organomet. Chem.* **1992**, *423*, 415. JUBVUX: Knierzinger, A.; Schonholzer, P. *Helv. Chim. Acta* **1992**, *75*, 1211. LEGZOM: Pregosin, P. S.; Ruegger, H.; Salzmann, R.; Albinati, A.; Lianza, F.; Kunz, R. W. *Organometallics* **1994**, *13*, 83. LELKAO and LELKES: Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523. MQALPD: Deeming, A. J.; Rothwell, I. P.; Hursthouse, M. B.; Backer-Dirks, J. D. J. *J. Chem. Soc., Chem. Commun.* **1979**, 670. SEYPAN and SEYPER: Togni, A.; Rihs, G.; Pregosin, P. S.; Ammann, C. *Helv. Chim. Acta* **1990**, *73*, 723. VIXXIJ: Albinati, A.; Kunz, R. W.; Ammann, C. J.; Pregosin, P. S. *Organometallics* **1991**, *10*, 1800. YIGVIT and YIGVOZ: Pregosin, P. S.; Ruegger, H.; Salzmann, R.; Albinati, A.; Lianza, F.; Kunz, R. W. *Organometallics* **1994**, *13*, 5040. YUHRAU and YUHREY: Zehnder, M.; Neuburger, M.; von Matt, P.; Pfaltz, A. *Acta Crystallogr., C* **1995**, *51*, 1109.

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(26) ChelpG charges were determined for structures **4**−**11**, using a radius of 2.3 Å for palladium. Only group charges for heavy atoms (with attached hydrogens summed in) were used as reference data.

Chart 1. X-ray Structures Included in the Parametrization

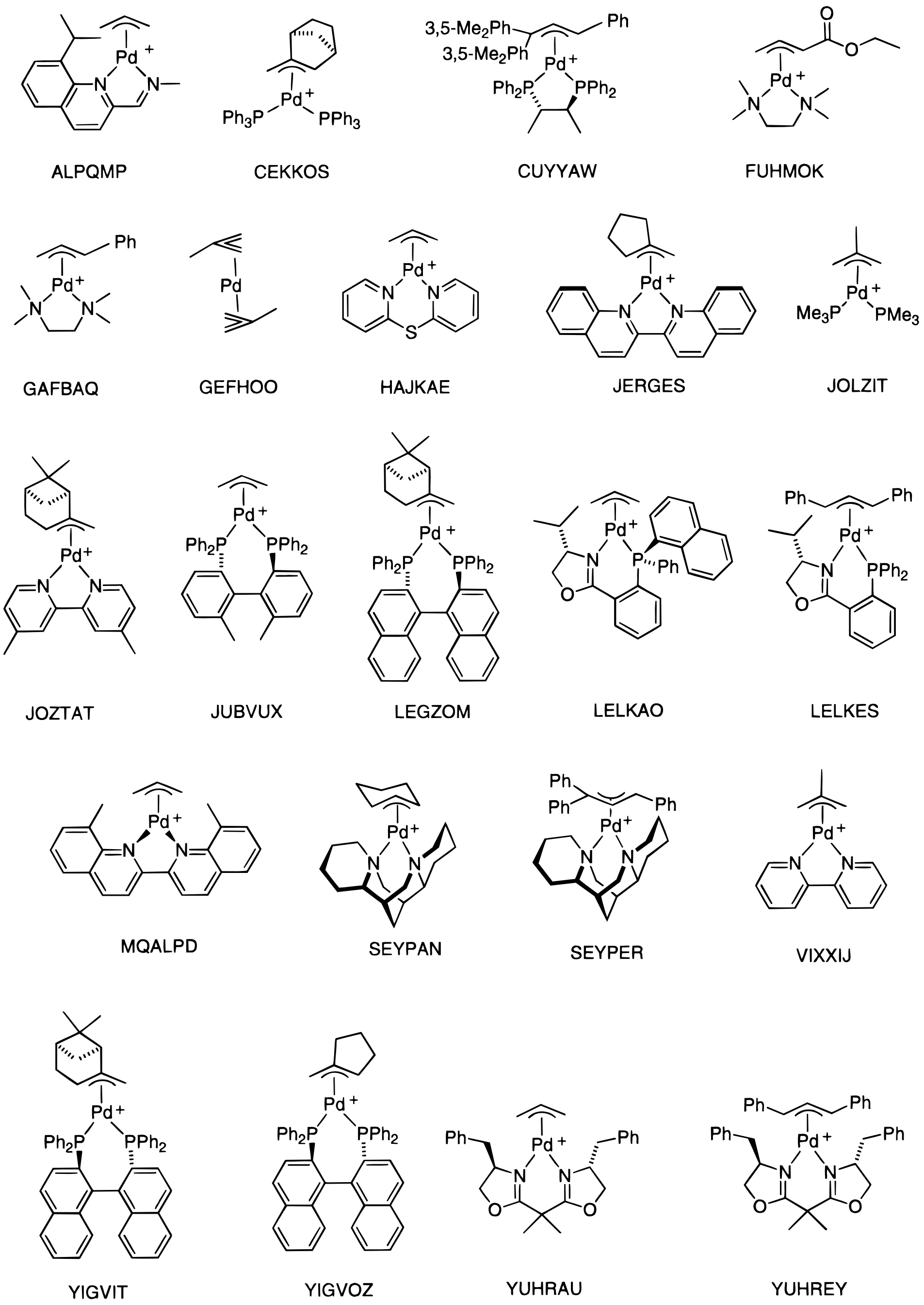


Chart 2. Quantum Chemical Structures Used in the Parametrization

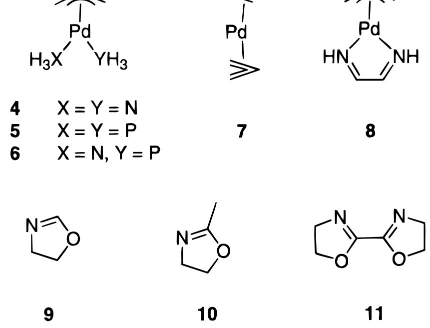
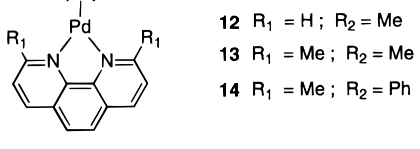


Chart 3. Structures Used for Calculating Relative Energies of Syn and Anti Complexes



tion. The experimental free energy differences were treated as simple steric energy differences, ignoring possible entropic and solvation contributions. The weight factors used for all reference data are given in Tables 1 and 2.

Parameter Optimization. To enable calculations on palladium allyl complexes with nitrogen and/or phosphorus ligands, over 200 parameters were added to the MM3* force

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Table 2. Weight Factors for Nonstructural Data

type of data	value	unit
relative energy	30[a]	[kJ^{-1} mol]
mass-weighted energy second derivative	0.002[b]	[kJ^{-1} mol Å^2 amu^{-1}]
CHelpG charges	50	[au^{-1}]

[a] 12 for one less well determined energy difference. [b] 0.150 for all atoms in a 1−4 relationship, see ref 24.

Table 3. Optimized Bond Stretching Parameters

bond type	l_0 [Å]	k$_s$ [mdyn/Å]
C_c−Pd	2.1304	4.7122*[b]
C_c−Pd [a]	2.1924	3.0070
C_c−C_t	1.3890	9.0974*
C_c−C_{sp3}	1.4971	5.2835
C_t−C_{sp2}	1.4622	4.5355*
C_t−C_{sp3}	1.4837	6.0518
Pd−N_{sp2}	2.0631	3.0783
N_{sp2}−H	1.0076	7.4152
Pd−N_{sp3}	2.1279	2.4717
N_{sp3}−H	1.0244	6.9630
Pd−P	2.2729	1.7665
P−H	1.4214	3.5819
C_t−H	1.0884	5.7292*
C_c−H	1.0877*	5.9136*
	Oxazoline Parameters	
Pd−N_{sp2}	2.0828	1.2818
N_{sp2}−C_{sp2}	1.2687	10.8014*
N_{sp2}−C_{sp3}	1.4710	10.6031*
C_{sp2}−O_{sp3}	1.3375	5.4548*
O_{sp3}−C_{sp3}	1.4455	6.2895*

[a] Applied when palladium carries phosphine ligand. [b] * = parameter not fully converged.

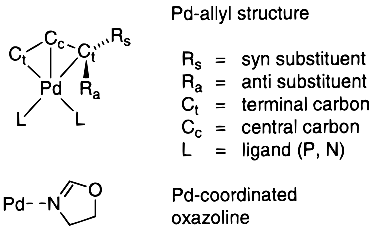

Figure 3. Palladium allyl notations and oxazoline structure used in the parametrization.

field. Adding parameters for stretching interactions (bond lengths and stretching force constants) and bending interactions (bond angles and bending force constants) is fairly straightforward, but care has to be taken when choosing the torsional interactions (dihedral angles and the corresponding force constants). Some torsions describe the intramolecular interactions better than others, and each can be controlled by up to three torsional constants. In particular torsions in small rings are highly redundant. Most torsional parameters were initially set to zero, whereupon a set of "chemically reasonable" parameters were selected for refinement. A few of these retained a value close to zero in the optimization and were subsequently removed.

In the parametrization it is important to have reasonable initial values of the parameters. It was especially important in our case because of the large number of parameters to be optimized. Initial parameters that are too far from their ideal values could result in a "false" optimum (to be compared to a local minimum in conformational searches) and would result in unnecessary time-consuming parameter refinement. The initial parameters were taken as averages from the relevant X-ray diffraction structures and from similar structures in existing force fields, the MM3* force field, the Allinger MM3 force field,[28] or the previously determined MM2 force field.[13] The van der Waals parameters for palladium, the radius and the hardness of the atom, were taken from the literature,[29] and the formal charge of palladium was set to +1.[30] The initial dipole moments were adjusted manually to give charges close to the ChelpG values.

To facilitate the handling of this large number of parameters in the parametrization, the parameters were divided into several subsets in such a way as to minimize the dependence between subsets. In doing so, the reference data could also be divided into subsets. For example, all X-ray structures with high-quality allyl geometries were extracted and used in a preoptimization of the allyl parameters. By the same approach, parameters for nitrogen sp^2 ligands, nitrogen sp^3 ligands, and phosphorus ligands were divided into three separate subsets and optimized using the relevant reference data. Other subsets handled the diallyl parameters, the allyl hydrogen parameters, allyl substituents, and the oxazoline ligand parameters. The preoptimizations on the smaller subsets gave better parameter values to use in the final total optimization. This saved time and reduced the risk of ending up in a local optimum. The smaller subsets were also much easier to handle and made it easier to check for the introduction of unreasonable parameter values.

All molecular mechanics calculations were performed using the MM3* force field in MacroModel Version 6.0 for Silicon Graphics workstations.[16] The parameters were optimized using a highly automated procedure described by Norrby and Liljefors.[19] Two optimization techniques were used in the parametrization. The subsets were initially optimized using a Simplex optimization. When the merit function of the force field[19] did not improve further in a reasonable number of steps, the parameters were subjected to a Newton−Raphson optimization. This was also the method used in the final total optimization. The optimization cycle was repeated until no further significant improvement of the merit function was obtained. Due to the high number of parameters, the force field was not fully converged. For a fully converged force field, the second derivatives of the merit function with respect to each parameter should be positive and also large when compared to the corresponding first derivative.[24] A few parameters in the final force field did not fulfill these criteria (vide infra).

To reduce the risk of ending up in a false optimum and to avoid unreasonable parameter values, parameter tethering was introduced in the parametrization. Parameter tethering can and should be used when an approximate value of a parameter is known, or when it is important that a parameter is kept within a certain known range. Tethering is also important when parameters are not uniquely defined by the data set. For example, bond angles were tethered to X-ray averages, to generate as strain-free structures as possible and also avoid the problem of redundancy (vide supra). Tethering is implemented as a weak harmonic constraint added to the merit function. The tethering constants ("optimum" value and force constant) used in the optimization are provided as Supporting Information.

Results

The optimized parameter values are given in Tables 3−7, using the notations of Figure 3. The parameters are presented according to type. The actual format used in the MM3* force field has been included as Supporting Information. As mentioned above, the force field is not fully converged. Thus, for a few parameters the post-

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(28) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551.

(29) Allinger, N. L.; Zhou, X.; Bergsma, J. *J. Mol. Struct. (THEOCHEM)* **1994**, *312*, 69.

(30) This choice allows the use of uncharged allyl and ligand moieties, while still getting the correct overall charge for all complexes except the diallyls. The actual charge on palladium is modified by the charge flux in the bonds to ligands.

Table 4. Optimized Angle Bending Parameters

angle type	θ_0 [deg]	k_b [mdyn Å/rad^2]
$\mathrm{Pd-C_c-C_t}$	69.0433	1.8005
$\mathrm{Pd-C_c-C_{sp3}}$	117.9344	4.4183
$\mathrm{C_t-C_c-C_t}$	120.6793	1.6356*[f]
$\mathrm{C_t-C_c-C_{sp3}}$	121.7991	0.2365
$\mathrm{Pd-C_t-C_{sp2}}$[a]	102.6491	0.1769
$\mathrm{C_c-C_t-C_{sp2}}$[a]	124.8945	2.1145
$\mathrm{Pd-C_t-C_{sp2}}$[b]	109.0391	0.2555
$\mathrm{C_c-C_t-C_{sp2}}$[b]	123.3112	0.6392
$\mathrm{Pd-C_t-C_{sp3}}$[a]	105.5137	0.5286
$\mathrm{C_c-C_t-C_{sp3}}$[a]	119.0062	0.3468
$\mathrm{Pd-C_t-C_{sp3}}$[b]	116.0939	0.1869
$\mathrm{C_c-C_t-C_{sp3}}$[b]	114.8433	0.3813*
$\mathrm{C_{sp2}-C_t-C_{sp2}}$	120.7909	2.2108
$\mathrm{C_t-C_{sp3}-C_{sp3}}$	110.4711	0.3678
$\mathrm{C_c-C_{sp3}-C_{sp3}}$	108.1241	1.3631
$\mathrm{C_c-Pd-C_c}$[c]	180.0000	0.4770
$\mathrm{C_t-Pd-C_t}$[c,d]	180.0000	0.7024
$\mathrm{C_t-Pd-C_c}$[c]	112.4691	1.3122
$\mathrm{C_t-Pd-N_{sp2}}$[e]	96.8875	0.6397
$\mathrm{C_t-Pd-N_{sp2}}$[d]	177.0979	0.1905
$\mathrm{N_{sp2}-Pd-N_{sp2}}$	90.2648	0.2987
$\mathrm{Pd-N_{sp2}-C_{sp2}}$	131.0284	0.2901
$\mathrm{Pd-N_{sp2}-C_{sp3}}$	127.1765	0.9632
$\mathrm{Pd-N_{sp2}-H}$	124.6688	0.6415*
$\mathrm{C_{sp2}-N_{sp2}-H}$	115.8749	1.2330
$\mathrm{C_t-Pd-N_{sp3}}$[e]	96.7457	1.5264*
$\mathrm{C_t-Pd-N_{sp3}}$[d]	169.5481	0.5656
$\mathrm{C_c-Pd-N_{sp3}}$	136.4937	0.3042
$\mathrm{N_{sp3}-Pd-N_{sp3}}$	86.7897	0.0078
$\mathrm{Pd-N_{sp3}-C_{sp3}}$	109.4538	0.6635
$\mathrm{Pd-N_{sp3}-H}$	107.9033	0.7371
$\mathrm{C_t-C_c-Pd}$[d]	70.3393	1.5839
$\mathrm{C_t-Pd-P}$[e]	90.7628	1.1096
$\mathrm{C_t-Pd-P}$[d]	171.7992	0.7583
$\mathrm{C_c-Pd-P}$	132.3992*	0.5286
$\mathrm{P-Pd-P}$	100.4825	0.6167
$\mathrm{P-Pd-N}$	94.5051	0.7456
$\mathrm{Pd-P-C_{sp2}}$	111.5180	1.2498
$\mathrm{Pd-P-C_{sp3}}$	113.8304	1.3922
$\mathrm{Pd-P-H}$	115.3164	1.5410*
$\mathrm{Pd-C_c-H}$	115.8790*	0.1986
$\mathrm{C_t-C_c-H}$	118.1611*	0.6393*
$\mathrm{Pd-C_t-H}$[a]	100.9212	0.7998*
$\mathrm{Pd-C_t-H}$[b]	118.4384	0.8538
$\mathrm{C_c-C_t-H}$[a]	118.5671*	0.2842
$\mathrm{C_c-C_t-H}$[b]	120.0842	0.0526
$\mathrm{H-C_t-H}$	116.5242	1.1511*
$\mathrm{H-C_t-C}$	117.0548	0.2532
Oxazoline Parameters		
$\mathrm{Pd-N_{sp2}-C_{sp2}}$	127.2735	0.3690
$\mathrm{C_{sp2}-N_{sp2}-C_{sp3}}$	116.5676	0.8120*
$\mathrm{N_{sp2}-C_{sp2}-O_{sp3}}$	126.1260	0.7693
$\mathrm{N_{sp2}-C_{sp2}-C_{sp2}}$	126.4541	0.5377
$\mathrm{N_{sp2}-C_{sp2}-C_{sp3}}$	128.9152	0.3205
$\mathrm{O_{sp3}-C_{sp2}-C_{sp2}}$	118.5661	1.6642
$\mathrm{O_{sp3}-C_{sp2}-C_{sp3}}$	118.5277	0.4449*
$\mathrm{C_{sp2}-O_{sp3}-C_{sp3}}$	112.6583*	0.4766

[a] Anti Substituent. [b] Syn Substituent. [c] Different allyl moieties. [d] Trans relationship. [e] Cis relationship. [f] * = parameter not fully converged.

refinement analysis indicates that small improvements in the merit function might be obtained by further modification[24] (these parameters are indicated with an asterisk in the parameter table). In all cases, these are parameters that are either unimportant to our goal (i.e., parameters needed for the QC model systems, but not present in any experimental structures) or where we lack sufficient high-quality data.

In the course of the optimization some force constants were zeroed and were thus automatically excluded from the optimization. The corresponding geometrical parameter was then manually set to an X-ray average value and thereafter excluded from further refinement. These parameters are given separately (Table 8).

A few parameters were taken from the MM3(94) force field[31] and used without further refinement. These parameters are given in Table 9.

Table 5. Optimized Torsional Parameters

dihedral angle type	v term	[kcal/mol]
$\mathrm{Pd-C_t-C_c-C_t}$	v_3	1.0620*[c]
$\mathrm{C_t-C_c-C_t-C_{sp2}}$	v_1	−1.5954
$\mathrm{C_t-C_c-C_t-C_{sp2}}$	v_2	5.6159
$\mathrm{C_t-C_c-C_t-C_{sp3}}$	v_1	−1.1671
$\mathrm{C_t-C_c-C_t-C_{sp3}}$	v_2	6.1413
$\mathrm{C_{sp3}-C_c-C_t-C_{sp3}}$	v_2	1.9589
$\mathrm{C_c-C_t-C_{sp2}-C_{sp2}}$	v_2	0.8961
$\mathrm{C_c-C_t-C_{sp2}-O_{sp2}}$	v_2	11.7507*
$\mathrm{C_c-C_t-C_{sp2}-O_{sp3}}$	v_1	0.5821*
$\mathrm{C_c-C_t-C_{sp2}-O_{sp3}}$	v_2	6.0264
$\mathrm{C_c-C_t-C_{sp2}-O_{sp3}}$	v_3	−0.0086*
$\mathrm{C_c-C_t-C_{sp3}-C_{sp3}}$	v_2	3.3701
$\mathrm{C_c-C_t-C_{sp3}-C_{sp3}}$	v_3	−1.7639*
$\mathrm{C_t-C_t-Pd-N_{sp2}}$	v_2	0.8475
$\mathrm{C_t-Pd-N_{sp2}-C_{sp2}}$[a]	v_2	0.1034
$\mathrm{C_t-Pd-N_{sp2}-C_{sp2}}$[a]	v_3	−0.2588
$\mathrm{C_t-Pd-N_{sp2}-C_{sp3}}$[a]	v_3	−0.5506
$\mathrm{C_t-Pd-N_{sp2}-H}$[a]	v_2	2.2627
$\mathrm{C_t-Pd-N_{sp2}-H}$[a]	v_3	1.9318*
$\mathrm{Pd-N_{sp2}-C_{sp2}-H}$	v_2	1.8068*
$\mathrm{Pd-N_{sp2}-C_{sp2}-H}$	v_3	−0.1089*
$\mathrm{Pd-N_{sp2}-C_{sp2}-C}$	v_2	1.6315
$\mathrm{Pd-N_{sp2}-C_{sp2}-C}$	v_3	2.4727
$\mathrm{C_t-C_t-Pd-N_{sp3}}$	v_2	1.8727*
$\mathrm{C_t-Pd-N_{sp3}-C_{sp3}}$[a]	v_3	−0.4103
$\mathrm{C_t-Pd-N_{sp3}-H}$[a]	v_3	−2.3194
$\mathrm{Pd-N_{sp3}-C_{sp3}-R}$[b]	v_3	0.9408
$\mathrm{C_t-Pd-P-C_{sp2}}$[a]	v_2	3.1012
$\mathrm{C_t-Pd-P-C_{sp2}}$[a]	v_3	0.8998
$\mathrm{C_t-Pd-P-C_{sp3}}$[a]	v_3	−2.4062
$\mathrm{C_t-Pd-P-H}$[a]	v_3	1.8611*
$\mathrm{C_t-C_c-C_t-H}$	v_2	5.1647
$\mathrm{C_t-C_c-C_t-H}$	v_3	0.6228*
Oxazoline Parameters		
$\mathrm{Pd-N_{sp2}-C_{sp2}-O_{sp3}}$	v_2	2.8599
$\mathrm{Pd-N_{sp2}-C_{sp2}-C_{sp2}}$	v_2	2.8950
$\mathrm{Pd-N_{sp2}-C_{sp2}-C_{sp3}}$	v_2	4.6543*

[a] Cis relationship. [b] Any atom. [c] * = parameter not fully converged.

Table 6. Optimized Charge Flux Parameters

atom 1	atom 2	dipole parameter[a] μ [debye]	charge flux[b]
Pd	$\mathrm{C_c}$	−3.7006*[e]	−0.36
Pd	$\mathrm{C_t}$	0.4480	0.04
Pd	$\mathrm{C_t}$[c]	0.3582	0.03
Pd	$\mathrm{C_c}$[d]	−3.5113	−0.33
Pd	$\mathrm{N_{sp2}}$	−3.5947	−0.36
$\mathrm{N_{sp2}}$	H	−0.1082*	−0.02
Pd	$\mathrm{N_{sp3}}$	−3.4184	−0.33
$\mathrm{N_{sp3}}$	H	−0.5633*	−0.11
Pd	P	−5.1330	−0.47
P	H	−0.6608	−0.10
$\mathrm{C_t}$	H	−0.6000	−0.11
$\mathrm{C_c}$	H	−0.6000	−0.11
Oxazoline Parameters			
Pd	$\mathrm{N_{sp2}}$	−3.5947	−0.35
$\mathrm{N_{sp2}}$	$\mathrm{C_{sp2}}$	−2.0609*	−0.34
$\mathrm{N_{sp2}}$	$\mathrm{C_{sp3}}$	−1.6885	−0.24
$\mathrm{C_{sp2}}$	$\mathrm{O_{sp3}}$	0.8189	0.13
$\mathrm{O_{sp3}}$	$\mathrm{C_{sp3}}$	−1.6079*	−0.23

[a] Not used as dipole internally. [b] The charge is added to atom 1 and subtracted from atom 2. [c] Used for palladium diallyl complexes. [d] Used when palladium carries phosphine ligands. [e] * = parameter not fully converged.

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(31) Several versions of MM3 are available from QCPE (web: http://www.chem.indiana.edu/qcpe.htm).

Table 7. Miscellaneous Parameters

parameter type	type	constant	unit
stretch bend	$Pd{-}N_{sp2}{-}C_{sp2}$	0.4005	[mdyn/rad^2]
out of plane bending	$N_{sp2}{-}Pd{-}C_{sp2}{-}C_{sp2}$	−0.0130	[mdyn/ang]
van der Waals interactions	Pd radius	2.0989	[Å]
van der Waals interactions	Pd eps	0.1970	[kcal/mol]

Table 8. Nonrefined Parameters

type of parameter	value	unit
$Pd{-}C_t$	2.1743	[Å]
$Pd{-}C_t{}^a$	2.2180	[Å]
$C_t{-}Pd{-}C_c$	37.6400	[deg]
$C_t{-}Pd{-}C_t$	67.3900	[deg]
$Pd{-}C_t{-}C_c$	70.7300	[deg]
$C_c{-}Pd{-}C_t{}^b$	142.4400	[deg]
$C_c{-}Pd{-}N_{sp2}$	137.5000	[deg]
$Pd{-}N_{sp2}{-}C_{sp3}{}^c$	125.7180	[deg]
Pd charge	+1	[au]

[a] Used for palladium diallyl complexes. [b] Different allyl moieties. [c] Applied for oxazoline ligands.

Table 9. Stretch-Bend Parameters Taken from MM3(94) and Used without Refinement

angle type	force constant [mdyn/rad^2]
any atom−N−H	0.0300
any atom−N−any atom	0.5719
any atom−O−H	0.0900
any atom−O−any atom	0.8778
any atom−S−H	0.0100
any atom−S−any atom	−0.0400
any atom−P−H	0.1000
any atom−P−any atom	0.0600

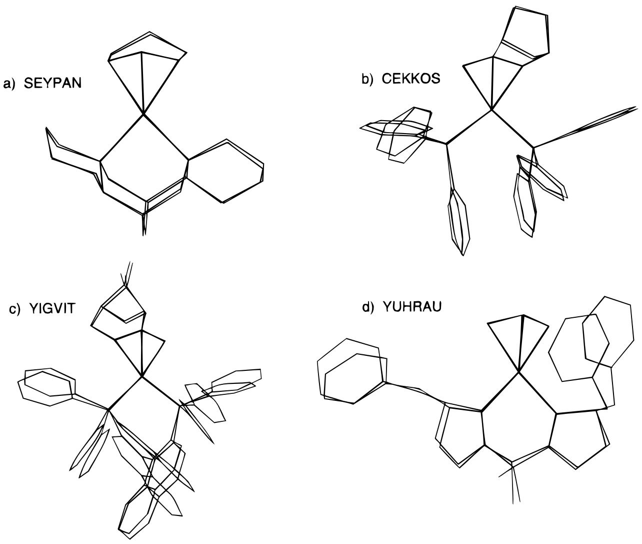

Figure 4. Overlays of palladium and directly attached atoms in X-ray- and MM3*- minimized structures.

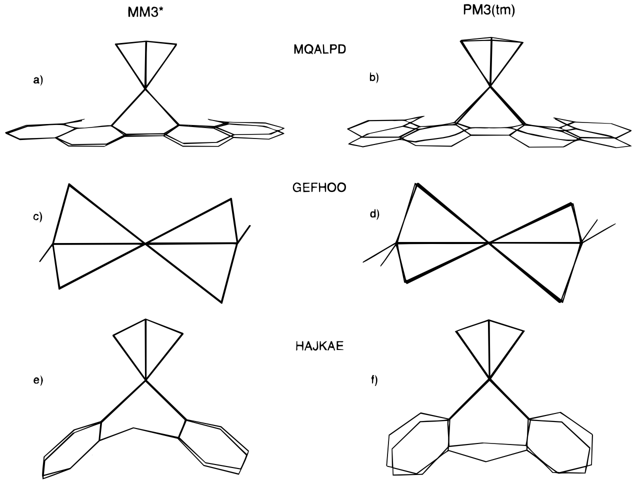

Figure 5. Overlays of palladium and directly attached atoms in X-ray- and minimized structures.

Validation. The first check for a new force field must be internal predictivity, that is, how well is the reference data reproduced by the calculations? As we have modified only parameters for moieties including or directly attached to palladium, only the local environment around palladium has been considered in the validation. The calculated structures are compared to the X-ray structures by a superposition of palladium and all atoms directly attached to palladium. Some selected structure overlays are shown in Figures 4 and 5. The rms values for the superpositions were calculated as a measure of the deviation from reference data. These rms values are given in Table 10 for all X-rays included in the parametrization.

The calculated relative energy differences of the few structures (**12**−**14**) included in the optimization are given in Table 11 together with the experimentally determined differences.

Another way of comparing the calculated structures to the reference X-ray structures is to calculate the energy excess.[24] The energy excess is defined as the difference in energy between a relaxed X-ray structure and the corresponding fully optimized structure. In the relaxed X-ray structure, the hydrogens are allowed to find their optimal positions, while the heavy atoms are held fixed. In MacroModel there are two ways of fixing the heavy atoms. One is to constrain the atoms in space by a harmonic tethering constant. A 500 kJ mol^{-1} Å^{-1} tethering force constant was used in this case. The heavy atoms should be allowed some relaxation to avoid a large influence of small bond deviations (within the experimental accuracy) in the structures. The other method freezes the atoms, holding them completely fixed. The latter method gives much higher excess energies, but was included to allow for a direct comparison with the results from our previous force field[13] or the PM3(tm) method (vide infra). The excess energies calculated using both of the above-mentioned methods are given in Table 12. The few excess energies calculated using the existing MM2 force field[13] are also included in this table.

For comparison, the X-ray structures were also minimized using the semiempirical PM3(tm) method and the Sybyl force field in the Spartan program package.[32] The rms values for these calculations are included in Table 10. The energy excess for most of the structures optimized using the PM3(tm) method was calculated and added to Table 12.

One structure (LELKES, **15**) was calculated by all available methods. Selected geometrical parameters from the various optimizations are compared in Table 13.

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(32) *Spartan* SGI Version 4.0.3 GL; Wavefunction Inc.: 18401 von Karman, Suite 370, Irvine, CA 92715, 1995.

Table 10. RMS Values from Superposition of Palladium and Directly Attached Atoms in X-ray and the Corresponding Structure Minimized Using Different Methods

X-ray	MM3	PM3(tm)	Sybyl
X-rays Included in the Parametrization			
ALPQMP	0.049	0.221	0.419
CEKKOS	0.054	0.073	0.368
CUYYAW	0.079	0.070	0.427
FUHMOK	0.042	0.097	0.370
GAFBAQ	0.035	0.109	0.362
GEFHOO	0.019	0.045	0.777
HAJKAE	0.032	0.072	0.323
JERGES	0.062	0.178	0.395
JOLZIT	0.042	0.054	0.364
JOZTAT_1	0.070	0.140	0.459
JOZTAT_2	0.057	0.140	0.483
JUBVUX	0.081	0.125	0.449
LEGZOM	0.073	0.104	0.439
LELKAO	0.063	0.082	0.395
LELKES	0.041	0.055	0.409
MQALPD	0.031	0.133	0.393
SEYPAN_1	0.063	*a*	0.327
SEYPAN_2	0.036	*a*	0.337
SEYPAN_3	0.060	*a*	0.325
SEYPER	0.037	*a*	0.850
VIXXIJ	0.035	0.093	0.440
YIGVIT	0.052	0.066	0.469
YIGVOZ	0.075	0.061	0.420
YUHRAU	0.052	0.066	0.423
YUHREY	0.058	0.071	0.383
X-rays Not Included in the Parametrization			
NANCIO	0.049	0.092	0.401
NANCOU	0.066	0.107	0.377
NANCUA	0.064	0.053	0.406
NANDAH	0.072	0.056	0.402
NOMVIU	0.049	0.055	0.377
REKVOS	0.062	0.122	0.447
RICMIZ	0.041	0.053	0.374
RIYGUB	0.060	0.053	0.410
ROMHEG	0.110	0.118	0.382
TAFKOA	0.064	0.153	0.441
TEYYAX	0.111	0.116	0.368
TISMAJ	0.063	0.078	0.416
TISMEN	0.066	0.058	0.406
TOQHUC	0.132	0.118	0.436
ZIBVUB	0.082	0.093	1.024
ZIQLOA	0.057	0.085	0.393

[a] Could not be optimized using PM3(tm) due to breakdown of the complex.

Table 11. Experimental and Calculated Energy Differences (kJ/mol)

structure	exptl	calcd
12	1.98	1.99
13	−5.44	−5.51
14	−8.60	−8.79

Discussion

The current parametrization includes the largest set of parameters attempted so far in our recently described automated procedure.[19] The bottleneck in the parameter refinement is a numerical differentiation of the merit function with respect to each parameter. Thus, each refinement cycle for the entire parameter set required more than a day on one processor of a modern SGI workstation. Division into subsets could be used to speed up the initial stages, but the final refinement stages had to include the entire set for full consistency. Nonetheless, the entire refinement cycle was only slightly more time-consuming than the determination of reference data (in particular the quantum chemical Hessians).

Table 12. Calculated Energy Excess Using Different Methods, for All Structures Included in the Parametrization

energy excess [kJ/mol]	frozen	constrained	MM2	PM3(tm)
ALPQMP	85	20	36.4	164.2
CEKKOS	41.5	24.6		129.1
CUYYAW	85.2	40.3		191.7
FUHMOK	111.8	25.8		128.3
GAFBAQ	15.9	6.4		95.7
GEFHOO	4.1	0.9		63.7
HAJKAE	14.5	5.1		107.6
JERGES	42.5	8.5	22.2	184.4
JOLZIT	29.3	11.4		74
JOZTAT_1	329.9	58.2		493.4
JOZTAT_2	226.8	42.7		328.4
JUBVUX	226.6	61.1		293
LEGZOM	300.3	75.6		340.1
LELKAO	116.6	29.6		160.1
LELKES	36.8	22.8		107.1
MQALPD	87.6	13.9	52.3	179.4
SEYPAN_1	102.2	33.6	49.4	350.9
SEYPAN_2	64.9	23.3		324.2
SEYPAN_3	54.1	21.1		327.7
SEYPER	348.9	92.1		660.9
VIXXIJ	19.8	7.1		112.8
YIGVIT	373.8	91.9		395.2
YIGVOZ	197.2	47.3		250.1
YUHRAU	42.2	17.8		186.9
YUHREY	49.7	24.5		185.3

Table 13. Important Geometrical Parameters for the LELKES X-ray, Calculated Using Different Methods

parameter[a]	X-ray	MM3*	Sybyl	PM3(tm)	QC	unit
Pd−C_c	2.164	2.190	1.953	2.230	2.258	Å
Pd−C_{t1}	2.137	2.198	1.974	2.158	2.171	Å
Pd−C_{t2}	2.237	2.231	1.972	2.191	2.399	Å
Pd−N	2.089	2.100	2.047	2.049	2.163	Å
Pd−P	2.274	2.259	2.284	2.271	2.353	Å
C_c−C_{t1}	1.402	1.397	1.636	1.451	1.437	Å
C_c−C_{t2}	1.397	1.397	1.638	1.430	1.396	Å
N−Pd−P	88.5	89.3	84.9	89.3	88.0	deg
Pd−C_{t1}−C	122.5	121.1	124.2	133.4	122.3	deg
Pd−C_{t2}−C	127.1	123.2	119.8	133.0	126.9	deg
C_c−C_{t1}−C	121.7	121.1	113.0	116.7	121.9	deg
C_c−C_{t2}−C	126.0	123.2	118.2	120.2	126.2	deg
C_{t2}−C_c−C_{t1}	119.1	120.6	115.6	117.0	121.2	deg
Δ[b]	0.100	0.033	−0.002	0.033	0.228	Å
rms		0.041	0.409	0.055	0.130	Å

[a] C_{t1} = Terminal allyl carbon trans to nitrogen. C_{t2} = Terminal allyl carbon trans to phosphorus. C_c = Central allyl carbon. C = Carbon of phenyl substituent. [b] Δ = (Pd−C_{t2}) − (Pd−C_{t1}).

The inclusion of a large number of reference data points is advantageous in a parametrization. The reference data should also be chosen according to the final use of the force field. It is usually insufficient to depend solely on crystal structure data. If a force field is to give reasonable values for the calculated energies, some type of energy data has to be included. A low number of experimentally determined relative energy differences can to some extent be counterbalanced by increasing the weight factors on these data, though the result might be at the cost of geometrical accuracy.

Inclusion of quantum chemical data is clearly beneficial. Quantum chemical calculations give reliable geometries and can be used in cases where X-ray structures lack accuracy, e.g. for hydrogen positions and soft torsions. Second, force constants can be determined with high accuracy using the energy second derivatives from a quantum chemical calculation. An alternative would be to fit experimental vibrational data (IR spectra), but for most real structures the problem of matching calculated normal modes to observed frequencies is almost insurmountable. Using calculated Hessians, the matching is trivial. B3LYP has generally been shown to give frequencies close to experiment and has been used here without scaling.[33] For cases where an exact match to experimental frequencies is critical, Dasgupta and Goddard have shown how experimental eigenvalues can be combined with calculated eigenvectors to yield a very high quality Hessian.[34]

The bond lengths and angles from the X-ray and B3LYP structures, the conformational energies, the B3LYP Hessians, and charges yielded a total of 11 145 data points for the 202 parameters included in the refinement. There are thus ca. 55 data points per parameter in the refinement. The data are also sufficiently varied to ensure that most parameters are well determined by the data. Nonetheless, a few parameters were not fully converged. This is, in part, because molecular mechanics parameters are by their very nature redundant. Consider the methane molecule as a very simple example. The angles can easily be reproduced by a reference angle of 109.47° and an arbitrary angular force constant (determined by fitting to vibrational data). On the other hand, the same structure would result if all angles were given higher reference values (e.g., 120°). The structure would then be very strained, but an automated procedure would find the latter parameter as easily as the former. The situation is more complex in larger molecules, but angles around the same center will always be redundant to some extent. This results in linear dependencies among the parameters and problems with convergence. It is usually considered advantageous to make the reference structures as strain-free as possible in the force field. Most angle reference values were therefore tethered by a weak harmonic constant to the average of the observed values, allowing a more rapid convergence. The refinement was terminated when new cycles no longer resulted in significant improvement.

Due to the high number of reference data points, the merit function is not expected to approach zero, which means that not even the reference data will be perfectly reproduced. To compensate for the lack of experimental energy data, it was necessary to use somewhat high weight factors to reproduce these ratios. The calculated values of the energy differences agree quite well with the experimental values in the final force field, as can be seen in Table 11. The weight factors used for the energy data may have had a negative influence on the geometrical accuracy, but, as can be seen in Table 10, most structures are fairly well reproduced by the force field. The agreement with the reference X-ray data is not perfect, but considering the high number of X-ray structures used, this may be difficult regardless. The balance between energy and geometrical accuracy in this case appears to be satisfactory.

Crystal packing forces may also cause deviations of calculated structures from X-ray diffraction data. Thus, care has to be taken when using X-ray data. These forces can to some extent give an improved balance between force constants, but only if a wide range of distortions is available for similar structural elements. The X-ray structure YUHRAU in Figure 4d shows an example where we believe that the major deviation, the rotation of the benzyl group, is due to crystal packing forces. In a validation of a force field, a complete superposition of reference structures and calculated structures is therefore an unreliable way of measuring the performance of the force field, unless the extent to which the crystal packing forces influence the structure can be estimated. A better evaluation would be to compare certain geometrical parameters such as bond lengths and angles. Rather than comparing all geometrical parameters for 25 X-ray structures, we chose to use a modified superposition of calculated and reference data. Instead of superimposing the whole structures, only palladium and atoms directly attached to palladium were superimposed. Thus, we avoid including any soft torsions or unrefined parameters in the test. The deviation is given in the form of an rms value for this superposition (Table 10). As can be seen, the agreement with reference data is very good, as shown by the low rms values. In Figures 4 and 5, some large deviations can be seen outside the local palladium environment. These are in general due to parameters already present in the force field and not modified by us. One example is Figure 4c (YIGVIT), where we believe that the deviations in the ligand mainly are due to low-quality torsional parameters for the binaphthyl bond.

An estimate of the energy excess of the crystal structures compared to the optimized structures can be found in Table 12.[13,24] With an ideal force field and perfect experimental structures, any energy excess should be due only to crystal packing forces. The excess energies calculated by the force field should therefore have low values. It can be seen that the new force field consistently gives better results than the PM3(tm) method. There are only a few structures for which the results can be compared to the previous MM2 force field.[13] In general, the older force field seems better able to accommodate the crystal distortions. The interpretation of this result is not clear. One explanation could be that the force constants in the old force field are lower than those obtained from the QC results in the current work. However, it is more probable that the dummy atoms utilized in the old force field allowed more realistic distortions than the direct valence bond approach implemented here. For example, the allyl moiety is frequently observed to tilt in response to unequal steric interactions at the two termini, making one Pd−C bond shorter when the other is elongated. This tilting was easily accommodated in the old force field by a slight movement of a dummy atom, without changing any bond lengths. To achieve the same effect in a direct valence bond model, it would be necessary to include a stretch−stretch interaction, something which cannot currently be done within the MacroModel package. It is noted that the removal of the dummy atoms in this work was not done to achieve higher accuracy, but rather to make the force field easier to use. We know that we have achieved the latter, but it seems this has been done at a slight cost in accuracy. However, for most

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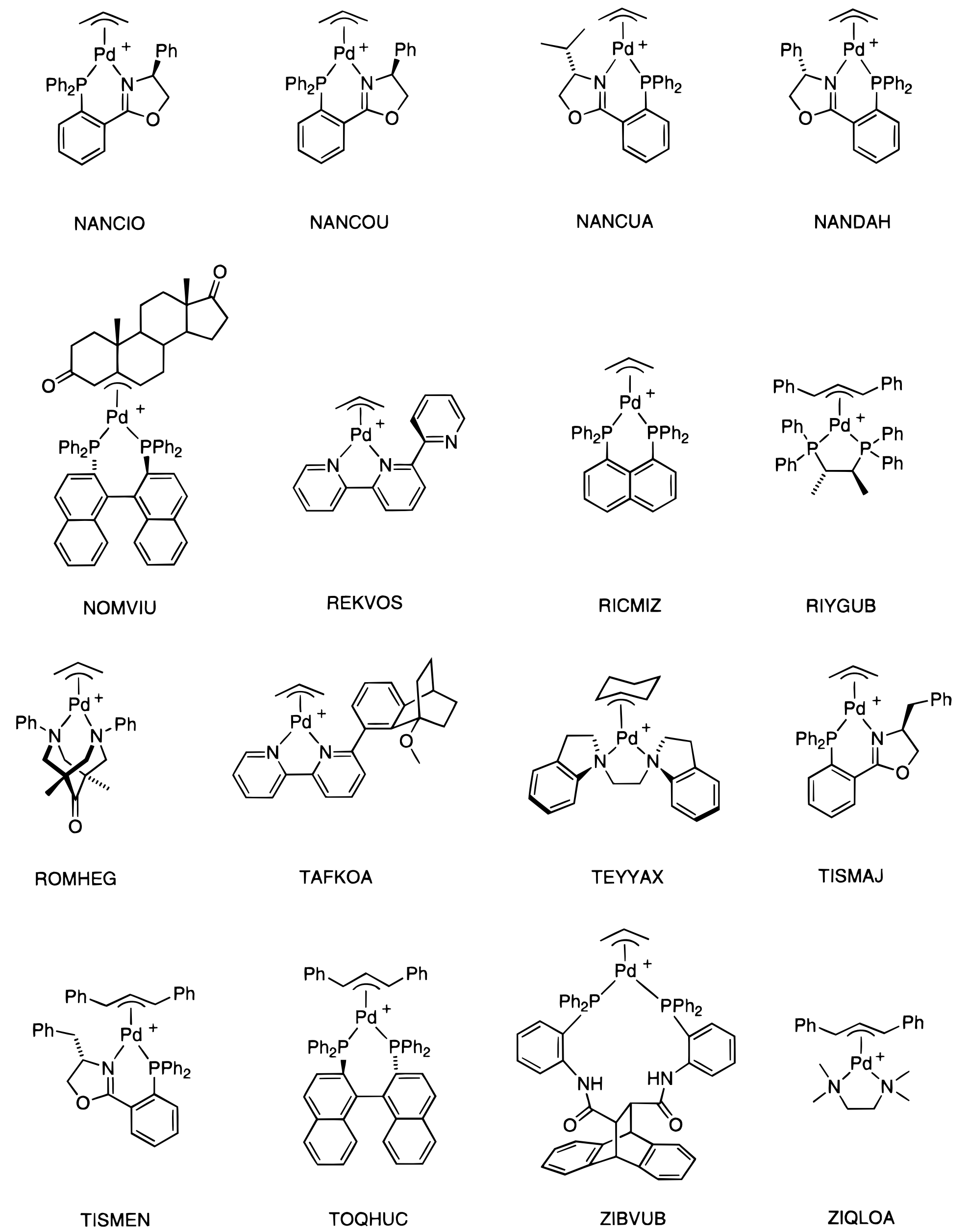
[33] The recommended scaling factors for determination of ZPE and thermodynamic vibrational contributions at the B3LYP/6-31G* level are very close to unity: Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.

[34] Dasgupta, S.; Goddard, W. A., III *J. Chem. Phys.* **1989**, *90*, 7207.

Chart 4. X-ray Structures Not Included in the Parametrization



NANCIO NANCOU NANCUA NANDAH

NOMVIU REKVOS RICMIZ RIYGUB

ROMHEG TAFKOA TEYYAX TISMAJ

TISMEN TOQHUC ZIBVUB ZIQLOA

applications, we believe the current force field to be sufficient.

More interesting in the evaluation of a force field is the agreement with data that has not been included as reference data in the parametrization. Some recently reported X-ray structures (Chart 4) from the Cambridge Crystallographic Database[35] were therefore minimized using the new force field. The rms values for these are given in the lower part of Table 10. As can be seen, the rms values for these structures are also satisfactory. Only in a few cases are the rms values higher than 0.1.

A few selected structures are shown in Figure 6. Structures NANCIO (6a) and NANCOU (6b) are two very interesting X-rays. The only difference between these structures is the counterion. NANCIO has a PF_6^- counterion, and NANCOU has a BPh_4^- counterion. The effect of the counterion on the X-ray structure is shown in Figure 6c. When comparing this overlay of the two X-ray structures to overlays between each X-ray structure and the MM3* minimum (Figure 6a,b), it can be seen that the difference between the X-ray structures

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(35) The X-ray structures were taken from the Cambridge Crystallographic Database. Original Publications as follows: NANCIO, NANCOU, NANCUA, NANDAH: Schaffner, S.; Macko, L.; Neuburger, M.; Zehnder, M. *Helv. Chim. Acta* **1997**, *80*, 463. NOMVIU: Drommi, D.; Nesper, R.; Pregosin, P. S.; Trabesinger, G.; Zurcher, F. *Organometallics* **1997**, *16*, 4268. REKVOS: Ramdeehul, S.; Barloy, L.; Osborn, J. A.; De Cian, A.; Fischer, J. *Organometallics* **1996**, *15*, 5442. RICMIZ: James, S. L.; Orpen, A. G.; Pringle, P. G. *J. Organomet. Chem.* **1996**, *525*, 299. RIYGUB: Yamaguchi, M.; Yabuki, M.; Yamagishi, T.; Kondo, M.; Kitagawa, S. *J. Organomet. Chem.* **1997**, *538*, 199. ROMHEG: Gogoll, A.; Grennberg, H.; Axen, A. *Organometallics* **1997**, *16*, 1167. TAFKOA: Pena-Cabrera, E.; Norrby, P. O.; Sjogren, M.; Vitagliano, A.; De Felice, V.; Oslob, J.; Ishii, S.; O'Neill, D.; Akermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299. TEYYAX: Abu-Surrah, A. S.; Fawzi, R.; Steimann, M.; Rieger, B. *J. Organomet. Chem.* **1996**, *512*, 243. TISMAJ, TISMEN: Baltzer, N.; Macko, L.; Schaffner, S.; Zehnder, M. *Helv. Chim. Acta* **1996**, *79*, 803. TOQHUC: Yamaguchi, M.; Yabuki, M.; Yamagishi, T.; Sakai, K.; Tsubomura, T. *Chem. Lett.* **1996**, 241. ZIBVUB: Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386. ZIQLOA: Barbaro, P.; Pregosin, P. S.; Salzmann, R.; Albinati, A.; Kunz, R. W. *Organometallics* **1995**, *14*, 5160.

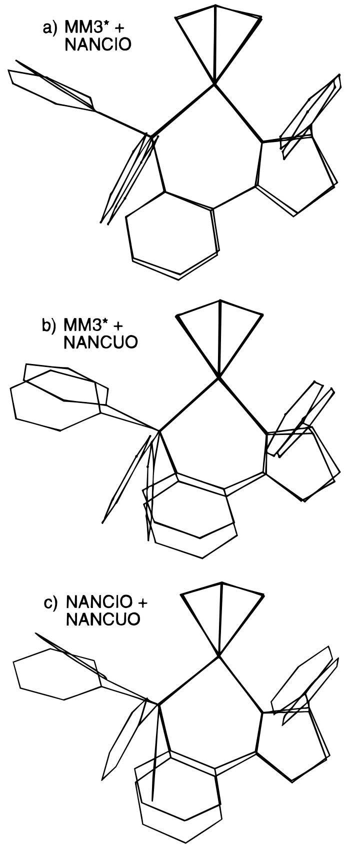

Figure 6. Overlays of palladium and directly attached atoms.

is greater than the difference between each X-ray structure and the calculated structure. The rms value for the overlay between the two X-ray structures is 0.071, to be compared with 0.049 and 0.066 for the overlays of the X-ray structure and the corresponding minimized structure. Thus, the deviation between calculated and reference data is no larger than the internal variation in the reference data set.

Comparisons between Methods. Computational structure determination methods can loosely be divided into molecular mechanics, semiempirical, and quantum chemical methods. Both molecular mechanics and semiempirical methods require parametrization against reference data. The accuracy of these methods is therefore very dependent on the reference data used.

Of the currently available force fields, only a few include parameters for organometallic compounds. Some force fields will use general parameters and thus allow calculations on these complexes even though they have not been specifically parametrized against this type of reference data. The Sybyl force field as implemented in Spartan belongs to this category. Among the semiempirical methods, the PM3(tm) method includes parameters for palladium. Semiempirical methods are considerably more time-consuming than molecular force field methods, but are more generally applicable when a particular element has been included. A direct comparison to the current force field is therefore of interest. Density functional (DFT) methods (in particular B3LYP) have lately emerged as the high-level method of choice for generating high-quality organometallic structures. In later years, the computational power available has increased to a point where experimentally interesting systems can be studied by these methods. In the current work, B3LYP calculations have been used to generate data for the parametrization. It is therefore highly interesting to compare the results of direct B3LYP calculations to the force field results. One structure, LELKES (**15**), was optimized using this method and compared to the results of the other methods.

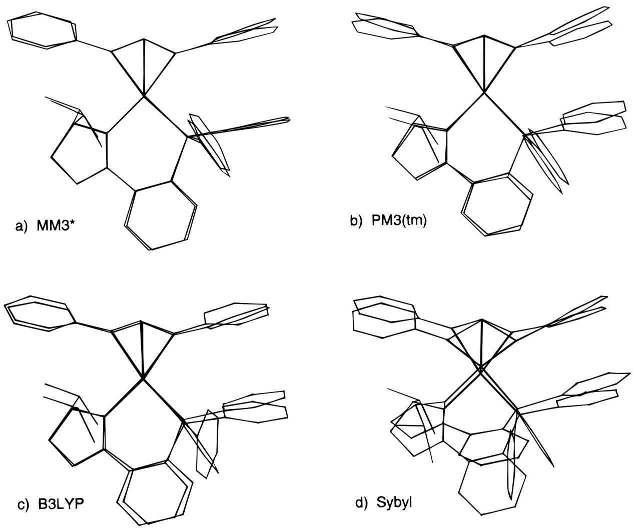

Figure 7. Overlays of palladium and directly attached atoms in the X-ray of structure **15** and the corresponding structure minimized using different methods.

Figure 7 shows a typical overlay of a structure minimized using the Sybyl force field in the Spartan program package[32] and the corresponding X-ray structure. The rms values for all the Sybyl calculations are included in Table 10. As can be seen from these results, the Sybyl force field has a serious problem with reproducing the allyl moiety. This is also reflected in the rms values of Table 10. The GEFHOO structure, for example, has an extremely high rms value and cannot be reproduced with this force field. We note that no specific (η^3-allyl)palladium parameters were used in the Sybyl optimizations, only the generic parameters delivered with Spartan. Thus, to make any valuable predictions from calculations on these complexes, it is clear that specific palladium parameters are needed.

A few of the optimized structures using the PM3(tm) method in Spartan[32] are shown in Figure 5. The structures in this figure are, as before, a superposition of palladium and directly attached atoms of the minimized structure and the corresponding X-ray structure. As can be seen in Table 10, the PM3(tm) method gives lower rms values than the force field only in a few cases. Apart from being more time-consuming, there are a few features in the π-allyl that the PM3(tm) method has difficulty in reproducing correctly. The first is the bending of the allyl out of the ligand plane in some of the structures, especially MQALPD (Figure 5b). Another is the angle that allyl substituents form with the plane of the π-allyl; see structure GEFHOO (Figure 5d). The force field described in this paper does not have these problems and is notably faster. In the time required for a PM3(tm) optimization of one structure geometry, a conformational search including several hundred structures could be carried out with the molecular mechanics method.

The LELKES structure (**15**) was optimized with the commonly used B3LYP method and the LANL2DZ basis set augmented with one d-function for atoms coordinated to palladium.[36] The results of the geometry optimizations using the different methods are shown in Figure 7. A few of the most important geometrical parameters, together with the rms values for the overlays, are given in Table 13. The modified MM3* force field handles the structure quite well, though there are some deficiencies. As expected, the differences in palladium to terminal carbon bond distances, depending on whether the carbon is cis or trans to the phosphorus, are underestimated by the force field (Table 13, second to last entry). However, this is also true for the semiempirical PM3(tm), while the B3LYP method overestimates this difference. One important observation is that the quantum chemical calculations overestimate the length of all bonds to palladium, while other bond lengths are well represented. This could in part be due to a basis set imbalance in the calculations, but it is interesting to observe that the force field, which is based on B3LYP force constants for small model systems, does not encounter these difficulties.

Summary

The force field was developed to study the palladium-catalyzed asymmetric allylic alkylation reaction (Figure 1). A considerable number of palladium allyl complexes can be handled with the new force field. The force field is particularly well suited for studying reactions in which steric interactions are believed to be the main factor controlling the stereochemical outcome, for example, in systems where C_2-symmetric ligands induce chirality through a chiral pocket. It can be used to study trends in reactions and effects of small structural changes in the ligands and thereby hopefully be useful in predicting the outcome of reactions.

The accuracy of molecular mechanics calculations on organic compounds has been shown to be high.[18] The accuracy of a modified force field will certainly depend on the added parameters, the reference data used, and the systems studied. It should be noted that none of the original MM3* parameters have been modified by us, though modification of some less well determined parameters might have improved the performance of the force field for our reference structures.

The force field reported herein can be used in prediction of selectivity in the palladium-assisted allylation reaction, as has been described previously.[8] Together with a force field for palladium olefins,[37] the force field can be used in the Jensen method[38] for identification of transition-state structures by extrapolation and intersection of the two force fields.

Direct studies of the transition state in the reaction of η^3-allyl systems have proved very hard. It is only recently that the transition state for this reaction has been identified using quantum mechanics.[10] The influence of solvent on this transition state has also been studied theoretically and was shown to be of paramount importance.[11] With the identification of transition states using quantum chemical calculations for small model systems, molecular mechanics determinations of transition-state geometries can be made possible.[39] Work is in progress to use the quantum chemical transition state data in the development of a molecular mechanics force field that can handle transition-state geometry optimizations.

With the current form of the force field, expansion for inclusions of parameters for other ligands such as oxygen, sulfur, or chloride is also made relatively easy.

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Supporting Information Available: A listing of force field parameters in MacroModel format, tethering values used in the parameter refinement, and overlays of all calculated and experimental structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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[36] We are grateful to Mats Svensson for giving access to the calculated structure of LELKES. Exponents for the added d-functions are as follows: P, 0.37; N, 0.80; C, 0.75.

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