Steric Influences on the Selectivity in Palladium-Catalyzed Allylation

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The product distribution from nucleophilic attack on (η^3-allyl)palladium complexes is analyzed by a combination of molecular mechanics and QSAR techniques. A predictive model has been derived from a training set carefully chosen to minimize effects from solvent, nucleophile, and electronic influences in allyl and ligand. The model shows good cross-validated predictive power and has been used to evaluate the relative importance of different steric influences on regio- and stereoselectivity in the title reaction.

Introduction

During the last few decades, the use of metal catalysts with chiral ligands has become a very versatile method in asymmetric synthesis.[1] Of particular interest to us is the palladium-catalyzed allylation reaction,[2−4] where several chiral bidentate ligands have been found to be efficient inducers of enantioselectivity.[4−16] Initially, most ligands were of the phosphine type,[5−7] but more recently dinitrogen ligands have been found to give good results in enantioselective allylations.[8−11] Very high enantioselectivity (>99%) has been achieved with C_2

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symmetric dinitrogen ligands.[10] There has also been much recent interest in combination ligands composed of one chiral unit (commonly a nitrogen ligand) that is supposed to induce selectivity and a second moiety (e.g., a phosphine), not necessarily chiral, that enhances reactivity.[11−14] Several of the PN ligands reach an enantioselectivity of 98% or better.[11,12] Very recently, an enantioselectivity exceeding 99% has for the first time been realized with an unsymmetric dinitrogen ligand in a catalytic reaction utilizing a ligand with two chiral centers of different types.[15]

The reaction mechanism of the palladium-assisted allylation is well understood. The leaving group in the allylic substrate is first displaced by Pd(0), forming an (η^3-allyl)palladium complex which can usually be isolated. Nucleophilic attack at one of the allyl termini will result in the final product and regeneration of the Pd(0) catalyst. With the most commonly utilized nucleophiles (e.g., malonates) and leaving groups (e.g., carboxylates), both the oxidative addition and the nucleophilic attack occur with inversion, leading to overall retention in the absence of isomerization in the intermediate.[4] There is a delicate balance between the various steps in this reaction.[16] Both the rate-limiting and selectivity-determining steps may vary, and they need not be the same. For example, in desymmetrization of substrates with two enantiotopic allylic acetates, transfer of chiral information may only take place in the oxidative addition step, irrespective of which step is actually rate limiting.[4c] For allyl monocarboxylates on the other hand, even if the oxidative addition step of a catalytic cycle is rate limiting, the nucleophilic addition may still be solely responsible for selectivity. This is the case with symmetrically substituted allyl moieties (e.g., **a** or **c**, Chart 2). Here the only selectivity possible is a differentiation of reactivity between the allyl termini. Other allyl moieties may loose any selectivity induced in the oxidative additon step through rapid syn−anti equilibria prior to nucleophilic addition.[4,17]

The possible modes of stereoselection in palladium-catalyzed allylation have been the basis of a recent review.[4c] In many cases, in particular in reactions with the substrate that has become the *de facto* standard test in the field, 1,3-diphenyl-2-propenyl acetate, product selectivity is determined in the nucleophilic addition step.[4] The product distribution pattern resulting from nucleophilic addition to (η^3-allyl)palladium complexes has been extensively studied, both experimentally by analyzing the structure, charge distribution, and expected trans effects in the intermediate[18] and quantum chemically at different levels of theory.[19]

We showed earlier that substituted phenanthroline ligands can be used to control the stereochemistry of (η^3-allyl)palladium complexes and their reactions with nucleophiles.[8,20] We have also shown that the stereochemistry and the preferred conformations of these and related[21] intermediate (η^3-allyl)palladium species may be rationalized by molecular mechanics using a recently developed parameter set for (η^3-allyl)palladium complexes.[22] It was possible to predict the product distribution from nucleophilic attack on the (η^3-allyl)palladium

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Chart 1. Substituted Phenanthrolines Used as Ligands in Palladium-Assisted Allylation

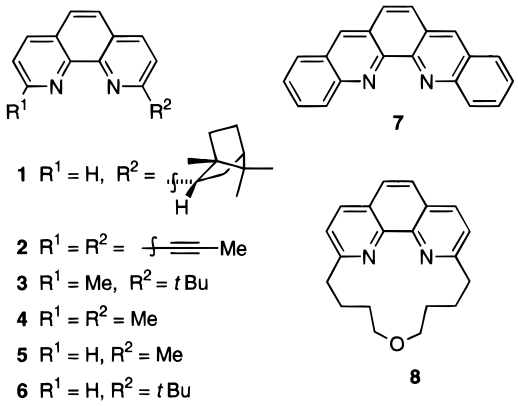
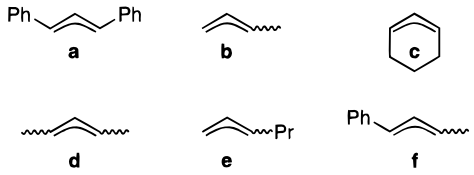


Chart 2 η^3-Allyl Moieties Considered in This Work



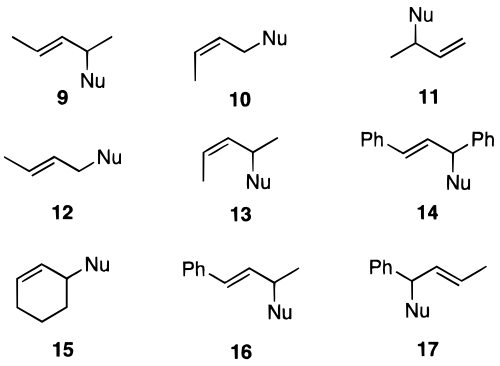
complexes in a qualitative sense and thus use the model in rational ligand design.[8] To take these studies one step further, we herein report an attempt to quantify the purely steric influences on the nucleophilic addition step in the title reaction. This is done by correlation of experimental selectivities with steric factors calculated using the previously developed molecular mechanics force field.[22]

Methods

It is known that several factors, such as the solvent and nature of the nucleophile, can alter the product pattern in palladium-catalyzed allylations.[6] However, in this paper we focus only on steric factors as one part of the overall problem. In elucidating the purely steric component of the selectivity, it is therefore imperative to utilize a data set where factors other than size and shape of ligand and allyl moieties are held constant. It is also important that the computational method has been validated for the structures in the data set. A third, less obvious requirement is that selectivities within the data set should not be too high. The reason for this is that we will attempt to fit a linear model to free energies of activation, which may be obtained from the product distribution pattern. A low selectivity may give a very accurate free energy difference, whereas a very small amount of the minor product isomer will lower the accuracy of the determination, with a corresponding large uncertainty in the observed free energy difference of the paths. Fortunately, we had at our disposal a set of data ideally suited for the current approach (Charts 1−3).

The phenanthroline moiety present in all ligands used in this study has been central in the development of the current force field. It has been shown that extreme distortions of the palladium allyl moiety are well reproduced for these and for the very similar class of bipyridine-type ligands.[22] There is also no electronic bias for attack at either allyl terminus, as the two ligand nitrogens are electronically very similar. In the unsymmetrically substituted ligands in the present study (**1**, **5**, **6**), one side of the ligand is unsubstituted whereas the other has an alkyl substitutent, but the remote electronic difference between hydrogen and alkyl may be safely ignored in the present study. Sterically, the substituents on the chosen ligands cover a large range of interactions with the allyl moiety, from the generally bulky *tert*-butyl group of **6** and the benzo-fused rings of **7** with its very specific interaction in the aromatic plane to the long, narrow propynyls of **2** and, of course, the small hydrogen. Most of the ligands are also very rigid, which drastically reduces the conformational search problem.

Chart 3. Isomeric Products Obtained from Allylic Substitution



A few potential problems in the set of allyl moieties must be considered. First, there is a potential electronic bias in allyl **f**, which has one alkyl and one phenyl substituent. This moiety is also unique in the data set in that there can be no crossover between enantiomeric pathways through the syn−anti isomerization. A change in configuration at one allyl terminus must also be accompanied by a change in *E*/*Z* configuration of the product double bond, unless isomerization pathways other than syn−anti exchange are in operation. It should be noted that other isomerization paths have been suggested,[23] but they are not expected to be fast relative to nucleophilic attack under the currently employed conditions.

Another problem is posed by allyl **e**, with a propyl substituent. It is entirely possible to find all conformations of this allyl, but inclusion of a very large number of conformations in the QSAR-type treatment to be utilized (*vide infra*) will detract substantially from the precision in the mathematical treatment. As it has been shown that product distributions are very similar from hexenyl and butenyl allyls (**e** and **b**, Chart 2),[16] a butenyl moiety was used in the calculations where experimental data was obtained for hexenyl.

Allyls **a** and **c** and the phenyl-substituted carbon in **f** were assumed to maintain a constant configuration.[24] Alkyl-substituted carbons (except in **c**) were assumed to undergo rapid syn−anti exchange. All structures were also assumed to undergo rapid syn−syn, anti−anti isomerization (i.e., apparent rotation of the allyl moiety, a process shown to be very rapid for the current class

(23) (a) Granberg, K. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 6858. (b) Nilsson, Y. I. M.; Andersson, P. G.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1993**, *115*, 6609. (c) Martin, J. T.; Oslob, J. D.; Åkermark, B.; Norrby, P.-O. *Acta Chem. Scand.* **1995**, *49*, 888.

(24) For phenyl groups, the anti position is strongly disfavored, even in environments known to favor the anti position. No *Z* product has been observed from **a**.

of complexes[17c]). Under these assumptions, product distribution should be unaffected by whether the reactions are run catalytically, or stoichiometrically from an isolated Pd−allyl complex. This point has been verified in several cases. All experimental data points are obtained with one nucleophile (diethyl methylmalonate) in one solvent (DMF), thereby minimizing influences from nonsteric factors.

It was postulated that the reactivity of a terminal allyl carbon (i.e., the free energy of activation for nucleophilic attack) can be described by a linear free energy relationship (LFER) based on calculated structure factors (eq 1). In eq 1, the descriptors x are calculated structural elements, including lengths of bonds to palladium, N−Pd−C bond angles, and various dihedral angles describing the position of the allyl relative to palladium and the ligand. The constants c are parameters to be determined by fitting to experimental data. Several such models were created and optimized by least-squares methods. The exact procedure is described in the Supporting Information.

$$\Delta G^* = c_0 + \sum_n c_n x_n \qquad (1)$$

Early on, it was found necessary to quantify the steric interaction with the incoming nucleophile. This quantification has traditionally been done by incorporating steric indices in the model.[25] However, with the molecular mechanics model available, we decided instead to measure the steric interaction energy by a probe technique. Thus, we chose an argon atom as a probe for the pure van der Waals component of the interaction with the incoming nucleophile. The steric probe was fixed along the vector of the reacting Pd−C bond at a distance of 3 Å from the the reacting carbon, whereupon the complex was reminimized.[26] The resulting energy increase was used as a descriptor x in the LFER model (eq 1).

It should be noted that setting all parameters c to zero in the LFER model does not correspond to a model giving equal selectivities for all products. Rather, it corresponds to setting the reactivity of all allyl termini equal and thus predicting a selectivity based on the Boltzmann distribution of the intermediates.[27] This "zero-level" model gives a small correlation coefficient $R^2 = 0.16$ with the experimental data set.

Each model was tested statistically in several different ways. In an absolute sense, the models were evaluated by use of the correlation coefficient, the F-test, and the C_p criterion.[28] The relative performances of different models were evaluated by partial F-tests. After the best model was chosen, the contributing descriptors were ranked according to the detrimental effect of deleting only that descriptor from the final model, as judged by partial F-tests. The relative importance of different descriptors was also evaluated from the correlation coefficients of optimized single-descriptor models. The final model was cross-validated and also validated by randomization of the input data.

Cross-validation (CV) is performed by exclusion of each data point (or group of data points) in turn, reoptimization of the model, and calculation of expected values for the excluded point(s).[29] From the error in these predictions, it is possible to calculate the cross-validated variance Q^2, which must always be lower than the correlation coefficient R^2 of the real model, but for a good predictive model, Q^2 should be significantly larger than zero. Values of 0.3 or 0.5 are commonly used as rules of thumb to indicate the lower limit of Q^2 where a model has significant internal predictive power. Two types of cross-validation were utilized, LOO (leave one out) and LSO (leave several out). In LOO CV, each data point is excluded and predicted separately, necessitating one full reoptimization of the model for each excluded data point. In LSO CV, the data were divided into four groups of three or four data points, chosen to maximize the diversity within each group (see Supporting Information).

The second validation model involves creating false input data for the model. The experimental selectivities are not altered, but redistributed among the structures in a random way. The model is then reoptimized and tested statistically (by F-test). If a randomized model can be shown to have significant correlation, the data set may be too small to allow proper identification of influencing parameters. The full randomization and reoptimization were performed 10 times for the final model.

The details of all statistical tests and validations can be found in the Supporting Information.

Results

The statistical evaluation indicated that four descriptors were needed to fit the experimental selectivities: the energy requirement calculated for the steric probe (*vide supra*), the bond length from palladium to the reacting carbon, and two dihedral angles describing a rotation−displacement of the allyl relative to the Pd−ligand moiety (*vide infra*). The final four-parameter model has a multiple correlation coefficient of $R^2 = 0.94$. From the F-test, we can also state that the model shows a statistically significant correlation with a confidence level greater than 99.999%. The calculated and experimentally observed selectivities for all data points in the study are shown in Table 1. Evaluation by partial F-tests show that any addition or deletion of a single descriptor to this model results in a significantly worse model,[30] with one exception (*vide infra*). Calculation of the C_p criterion for models resulting from single deletions also indicates that further deletions would be ineffective in increasing the significance of the correlation.

(25) Jurs, P. C.; Dixon, S. L.; Egolf, L. M. In *Chemometric Methods in Molecular Design*; Mannhold, R., Krogsgaard-Larsen, P., Timmerman, H., Eds.; VCH: Weinheim, Germany, 1995.

(26) The exact transition state geometry is not known, but a reaction trajectory has been postulated: (a) Trost, B. M.; Lautens, M. *Tetrahedron* **1987**, *43*, 4817. (b) The position of the probe in our calculations corresponds closely to that found in an investigation at the B3LYP/LANL2DZ level: Hagelin, H.; Åkermark, B.; Norrby, P.-O., manuscript in preparation.

(27) This is in fact a simple elaboration on the prediction method of Bosnich et al.[3]

(28) Kleinbaum, D. G.; Kupper, L. L.; Muller, K. E. *Applied Regression Analysis and Other Multivariable Methods*, 2nd Ed.; PWS-KENT: Boston, MA 1988.

(29) Wold, S.; Eriksson, L. In *Chemometric Methods in Molecular Design*; Mannhold, R., Krogsgaard-Larsen, P., Timmerman, H., Eds.; VCH: Weinheim, Germany, 1995.

(30) Adding any descriptor will always lead to a model with a better correlation coefficient R^2, but the partial F-test in all cases show that the correlation is less significant due to the larger number of degrees of freedom.

Table 1. Experimental and Calculated Isomeric Ratios of the Products in Palladium-Catalyzed Allylic Substitution

			product ratio		$\Delta\Delta G^*$/kJ mol^{-1}	
entry	complex	products	exptl[a]	calcd[b]	exptl[a]	calcd[b]
1	**1a**	(*S*/*R*)-**14**	2.23[c,d]	1.25	1.98	0.56
2	**1c**	(*R*/*S*)-**15**	3.50[c]	2.26	3.10	2.02
3	**1d**	(*S*/*R*)-**9**	1.27[c,d]	1.88	0.60	1.56
4	**1f**	**16/17**	2.30[e]	2.02	2.06	1.74
5	anti-**2b**	**11/10**	1.86[f]	1.32	1.53	0.70
6	**3b**	**10/11**	1.00[f,g]	1.02	0.00	−0.05
7	anti-**4b**	**11/10**	1.50[f,h]	0.83	1.00	−0.47
8	syn-**4b**	**12/11**	99.0[h]	98.9	11.4	11.4
9	**4d**	**9/13**	49.0	36.6	9.64	8.92
10	**4f**	**16/17**	10.1	8.11	5.73	5.18
11	**5f**	**16/17**	1.45[e]	1.53	0.92	1.05
12	**6f**	**16/17**	4.50[e]	11.3	3.73	6.01
13	**7b**	**10/11**	2.33[f,g]	0.84	2.10	−0.42
14	**8b**	**10/11**	3.27[f,g]	4.03	2.94	3.46
			rms $\delta\Delta\Delta G^*$/kJ mol^{-1}:			1.19

[a] Except where noted, results from catalytic reactions of *E*-allylic acetate with sodium diethyl methylmalonate in DMF, ref 19c. [b] T = 298 K. Syn−anti isomerization is assumed to be fast relative to nucleophilic attack in catalytic reactions and slow in stoichiometric reactions. For entries 5, 7, and 8, only conformers of one allyl isomer (syn or anti) were used in the calculations. [c] Result from ref 20. [d] Absolute configuration was not assigned. [e] This work. [f] Product **11** (internal attack) was assumed to result from attack on anti complex, cf. entry 8. [g] Experimental value for the hexenyl system, allyl **e**. [h] Stoichiometric reaction.

Addition of the length of the Pd−N bond trans to the reacting carbon as a descriptor resulted in a five-parameter model with a correlation coefficient R^2 = 0.95. A partial *F*-test showed only an 82% probability that the larger model had a more significant correlation, and both models yielded a C_p value lower than the number of parameters. Both models were therefore validated by LOO, by LSO, and with randomized input data.[29] The four-parameter model gave an LOO Q^2 = 0.86 and an LSO Q^2 = 0.87, whereas the five-parameter model gave an LOO Q^2 = 0.89 and an LSO Q^2 = 0.85. As the results with randomized input data also were similar for both models (see Supporting Information), it was not possible to judge between the two models based on performance. The four-parameter model was chosen as the final model for two reasons: First, it is prudent to base the interpretation on as few parameters as possible, to avoid overinterpretation. Second, when each descriptor was tested in optimized single-descriptor models, the extra parameter in the larger model (the Pd−N bond length) showed by far the worst performance, with a final correlation coefficient R^2 = 0.18 (compare to R^2 = 0.16 for the model without descriptors, *vide supra*). All descriptors in the final four-parameter model show correlation coefficients R^2 = 0.44−0.56 in single-descriptor models (see Supporting Information).

The cross-validated correlation coefficients calculated for the final model (LOO, Q^2 = 0.86; LSO, Q^2 = 0.87) show significant internal predictive power. The calculated values from the final model and the predictions from the LOO cross-validation are illustrated in Figure 1. In 10 different runs with randomly scrambled input data, one optimized model with a correlation coefficient R^2 = 0.68 was obtained. This "best" randomized model shows significant correlation at the 99% confidence level. However, an LOO cross-validation gave a Q^2 = −0.86, showing a complete absence of internal predictive power!

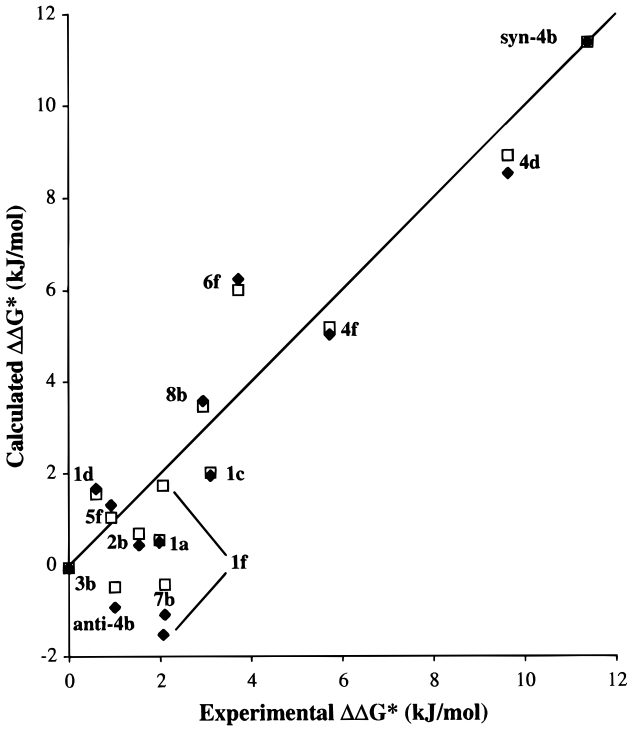


Figure 1. Correlation between calculated and experimental activation energy differences (kJ mol^{-1}) for product isomers. The values are labeled corresponding to the intermediate complexes (Charts 1 and 2, Table 1). Data points are indicated by (□) for calculations by the final model and (◆) for a predicted data point that was left out of the fitting procedure (LOO validation).

Discussion

Of the four parameters in the final model, the first and most important is the energy increase calculated when the structures are energy minimized with an added steric probe in the postulated transition state position for the nucleophile. This correlation is in complete accordance with previous results from Trost.[4,26a] The probe model as implemented here is very simplistic and takes no account of bonding and hybridization in the transition state. Thus, the calculated absolute energies are expected to be substantially larger than those actually experienced by the incoming nucleophile. This is indeed observed, the optimized factor in the final LFER model is ∼0.14, indicating that the calculated steric energy cost for the approach of the nucleophile is ∼7 times too high. It might be possible to find a probe that gives energies closer to the actual activation energies, but it is by no means assured that such a probe would give a better correlation with the observed *relative* reactivities. There is no doubt that the probe technique employed here accomplishes the current goals, namely, to identify the influence of the approaching nucleophile and to create a predictive model.

The second contribution comes from bond strain in the breaking Pd−C bond. To give a general idea of the magnitude of this effect, an elongation of the Pd−C bond by 0.01 Å will approximately double the reactivity at this carbon. The correlation has been observed earlier[4,11] and has been interpreted both in terms of relief of bond strain upon nucleophilic attack and as increased cationic character at the allyl terminus upon bond elongation. Of the final four parameters, this is the

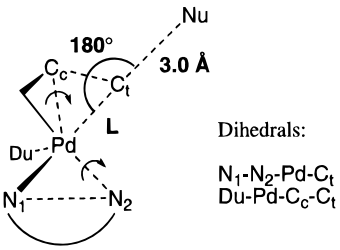


Figure 2. Descriptors in the final model. The "Du" pseudoatom is needed in the molecular mechanics description of the complex. The Pd−Du vector is approximately perpendicular to the average coordination plane.

least significant, as shown by single deletions and partial *F*-tests.

The last two significant effects are related to in-plane rotation and displacement of the allyl. The distortion in the model is described by two dihedral angles (Figure 2) but can most easily be visualized as a movement of the terminal carbon perpendicular to the coordination plane. The effect is weaker than that of the Pd−C bond elongation in that a larger distortion is needed for the same reactivity change, but also more important in that it gives a larger total contribution to the calculated selectivity (out-of-plane distortions in general have a much larger magnitude than bond elongation in the complexes in the current study). This effect has previously been recognized qualitatively and may be viewed as a distortion toward a more productlike structure.[4,8,11]

One specific cross-validation term needs to be discussed further. This is the result for complex **1f**, that is, the only complex in the study with both a chiral ligand and an unsymmetrically substituted allyl moiety. It is obvious from Figure 1 that this point is the sole representative in one portion of the descriptor space, as exclusion of this point in LOO leads to a noticeable change in the model. It should be emphasized that, with a small data set, a failure in internal prediction for this point need not affect the external predictive power. However, as this complex has some specific properties, it is prudent to investigate the cause of the (small) deviation further. As was discussed in the Introduction, the allyl moiety **f** is unique in that crossover between enantiomeric paths cannot take place by any of the recognized dynamic equilibria in the intermediate. In the modeling described so far, this fact has been ignored, and rapid equilibria between all isomeric forms of the intermediate (η^3-allyl)palladium complex have been assumed. We naturally assumed this to be the reason for the deviation in internal prediction for this complex, and the calculations were adjusted to give separate predictions for the enantiomeric starting material. However, no improvement in the predicted outcome could be obtained by this refined procedure. Thus, other reasons for the deviation should be considered. We have attempted to include a descriptor describing the electronic difference between an alkyl- and an aryl-substituted allyl terminus. However, no improvement in predictive power was obtained with the added parameter, and the good results for complexes of allyl **f** with nonchiral ligands also indicate that no such descriptor is needed. We will conclude by noting that only when the complex **1f** was excluded from the parameterization did the calculated value for **1f** deviate by ~3.6 kJ mol^{-1} from the experimental result. Obviously, the unique properties of complex **1f** within the small current data set are needed for proper parameterization. We should also comment that in molecular mechanics calculations, an error of 3−4 kJ mol^{-1} is in no way remarkable. In a recent comparison of some of the best molecular mechanics force fields in use today, the average error in conformational energy calculations was shown to be at least 1.5 kJ mol^{-1} for some simple organic compounds.[31] The maximum error of 3.6 kJ mol^{-1} and average absolute error of 1.4 kJ mol^{-1} in the LOO predictions for the organometallic system presented here is completely satisfactory in view of the expected errors in organic examples.

The current results have been obtained for a limited set of ligands and allyls, with just one nucleophile and solvent system. What, then, are the scope and limitations of the current model specifically and the methodology generally? As this study is, to our knowledge, the first attempt to quantify the separate steric influences on selectivity in metal-catalyzed reactions, the transferability to other systems cannot be judged with certainty. However, the trends in our conclusions agree well with previous proposals, which have been based on a large variety of ligand and allyl systems.[4,8,11] It is therefore reasonable to assume that, at least for electronically symmetrical ligands, the model should be applicable in the current form, if not for quantitatively accurate predictions, then at least for predicting trends. The fact that a simple change[8] of nucleophile from diethyl methylmalonate to diethyl malonate can shift the selectivity by 3−4 kJ mol^{-1} definitely indicates that quantitative predictions require reparameterization for each specific reaction system or extension of the model by inclusion of descriptors for solvent, nucleophile, temperature, and probably other factors also. However, in ligand design, predictions of *relative* selectivities for different ligands will often be sufficient.

The model as described here is also limited by the underlying molecular mechanics model. Predictions could in principle be based on other sources of structural data, but there are several reasons why the concept described here requires calculation of structures and energies. First, the importance of the steric energy increase upon nucleophile approach has clearly been demonstrated. Such a steric energy cannot easily be quantified other than by calculation. Second, it has been clearly seen in the modeling that it is necessary to include multiple conformations of the intermediate. X-ray crystallography, for example, will seldom give the structure of more than one form of the (η^3-allyl)-palladium complex, and there is no guarantee that the crystal structure corresponds to either the favored conformation in solution or the most reactive conformer. Finally, the current free-energy model has been based on the molecular mechanics calculated structures. In the fitting procedure, it is entirely possible that errors in the structures have been compensated for. Systematic errors may to some extent be cancelled, and in case the systematic errors are transferable to other structures, exclusion of these errors must lead to less accurate predictions. Thus, the two sets of parameters (molecular mechanics and LFER) should be viewed as a unit, and changes in the method of calculating

(31) Gundertofte, K.; Liljefors, T.; Norrby, P.-O.; Pettersson, I. *J. Comput. Chem.* **1996**, *17*, 429.

structures and energies should be reflected by corresponding changes in the LFER model. The *concept*, on the other hand, should be transferable to any reaction where structures and energies can be estimated accurately.

A final point concerns extension to systems with electronically differentiated ligands. There has been recent interest in bidentate ligands with one unit inducing asymmetry and the other being mainly responsible for increasing reactivity (but possibly also aiding in asymmetric induction).[11−14] One class of such ligands are the P−N bidentate ligands, with one phosphine and one nitrogen moiety.[11−13] The short bond between N and Pd facilitates chirality transfer, whereas phosphines are known to enhance the reactivity of palladium in the allylation reaction. Such systems can in principle be treated in two different ways. The most general method would be to introduce descriptors describing the electronic properties of the ligand trans to the reacting carbon, which is believed to be the most important for determining reactivity. However, a much simpler method would be to postulate that the nucleophile solely reacts trans to the activating ligand (e.g., P). This treatment would alleviate the need for additional descriptors, and also simplify the calculations, as only half the normal number of steric probe tests would have to be performed. The latter approach is currently being used in an attempt to predict the outcome of allylations with chiral ligands of the P−N type.[32] Work is also in progress to obtain more information about the nucleophilic addition transition state by high-level quantum chemical calculations[33] and to broaden the scope of the underlying molecular mechanics force field.[34]

Conclusions

This work presents a new tool for predicting regioselectivity and stereoselectivity and for evaluating the basis of this selectivity in palladium-assisted allylations. The method described accounts for steric effects in the nucleophilic attack step and makes it possible to reach useful conclusions about factors determining selectivity. Therefore, this method may be used both to gain a greater understanding of previously studied examples and to make predictions of the regio- and stereochemical outcomes of new cases. The present results are also consistent with metal−allyl, metal−ligand, and nucleophile interactions that have been hypothesized previously as important product-determining factors. The methodology described in this work is by no means limited to palladium-catalyzed allylation but should be applicable to numerous other reactions.

Experimental Section

General Details. 2-[(1*R*)-2-*endo*-1,1,7-Trimethylbicyclo-[2.2.1]hept-2-yl]-1,10-phenanthroline (**1**),[8] 2-methyl-1,10-phenanthroline (**5**),[35] 2-*tert*-butyl-1,10-phenanthroline (**6**),[20c] *trans*-4-phenyl-3-butenyl-2-acetate,[8] and bis(*μ*-trifluoroacetato)bis{(1,2,3-*η*)-2-butenyl}dipalladium[36] were prepared using literature procedures. All other chemicals were purchased from Aldrich, purified, and dried with standard methods.[37]

The isomeric ratios were determined using ^{1}H NMR (400 MHz, Bruker Model AM400) and GC (Varian 3700).

General Procedure for Palladium-Catalyzed Allylation. Bis(*μ*-trifluoroacetato)bis{(1,2,3-*η*)-2-butenyl}dipalladium (2.7 mg, 0.01 mmol), the phenanthroline derivative (0.05 mmol), and 1 mL of DMF were added to an oven-dried flask. A nitrogen atmosphere was established in the flask, and the flask was lowered into an ice bath. After the mixture was stirred for 10 min, 1 mmol of the allyl acetate was added together with 70 mg of the internal standard dodecane. Thereafter, 2 mL of a 1 M solution of sodium diethyl methylmalonate (2 mmol) in DMF was added, and the mixture was allowed to reach ambient temperature. The reaction was monitored by GC at regular time intervals (5 and 15 min and 1, 5, and 21 h) by working up a small aliquot in diethyl ether and H_2O. After completion, the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated. The products were purified by MPLC (silica gel) as described by Bæckström et al.[38]

Computational Details. All calculations were performed on Macintosh computers. Energy minimizations were performed with the MM2 program[39] utilizing a previously published parameter set for the (η^3-allyl)palladium moiety.[22] Steric probe calculations were performed as follows: starting from an energy minimized (η^3-allyl)palladium complex, an argon atom (Ar) was positioned 3 Å from the reacting carbon (C_R), with a Pd−C_R-Ar angle of 180°. The resulting complex was reminimized with Pd, C_R, and Ar held fixed. The difference between the minimized energies with and without the probe was used as a descriptor in the model. Statistical analysis and modeling were performed in Microsoft Excel.[40]

Acknowledgment. We thank Professor Tommy Liljefors for valuable discussions about statistical validation tools. Financial support from the Swedish Trygger Foundation, the Swedish Research Council for Engineering Sciences, the Danish Medical Research Council, the National Institutes of Health (U.S.A.), and the National Science Foundation (U.S.A.) is gratefully acknowledged. J.D.O. is grateful for a research scholarship from the Royal Institute of Technology.

Supporting Information Available: Basic methodlogy for LFER modeling, short force field description, definition of descriptors, and tables of statistical results for all LFER models tested, coefficients for the final LFER model, and validation results (9 pages). Ordering information is given on any current masthead page.

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(39) MM2(91), version for Macintosh: MacMimic/MM2(91), InStar Software AB, IDEON Research Park, S-223 70 Lund, Sweden. Memory allocation for external parameters was extended. MM2 versions for platforms other than Macintosh are available from the Quantum Chemistry Program Exchange, University of Indiana, Bloomington, IN 47405.
(40) Microsoft Excel 5.0 for Macintosh, from Microsoft Corp.