Nature of the Interactions between Polar β-Substituents and Palladium in η^3-Allylpalladium Complexes— A Combined Experimental and Theoretical Study

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Abstract: Deuteromethanolysis of six β-methoxy-substituted η^3-allylpalladium complexes (**1**–**5**) was studied under the same reaction conditions. The reaction rates depend on the ring size of the cyclic complexes, on the σ-donor/π-acceptor nature of the ancillary ligand, on the configuration of the allylic moiety, and on the position of the β-substituent with respect to the palladium atom. Replacement of the methoxy group proceeds about 1000 times faster in the *trans*-β-substituted cycloheptylallyl palladium complex **2** than in the cyclooctyl analogue **3**; this indicates that the C–O bond strength is a function of the ring and substituent conformations. A theoretical analysis of the structure and stability of slightly simplified model compounds **6**–**10** was performed with density functional theory at the B3PW91 level in order to elucidate the relationship between the rate of deuteromethanolysis and the electronic interactions between the β-methoxy substituent and the palladium atom. It was concluded that the strength of these β-substituent effects critically depends on the relative position of the Pd–C3 and C4–O bonds. In cyclohexyl and cycloheptylallyl complexes **6** and **7**, the *trans*-β-methoxy substituent adopts a conformation that is particularly favoured by the β-substituent effect. Since the η^3-allylpalladium complexes studied and their derivatives are key intermediates of important palladium-catalysed transformations, the implications of the β-substituent effect for the regio- and chemoselectivity of nucleophilic attack are also discussed.

Keywords
allyl complexes · chemoselectivity · density functional calculations · regioselectivity · stereoelectronic control · substituent effects

Introduction

Application of allylpalladium chemistry to organic synthesis made remarkable progress in recent decades.[1–5] In particular, palladium-catalysed reactions of allylic substrates and conjugated dienes with nucleophiles have became widely used preparative procedures,[6, 7] owing to their practical simplicity, versatility and potential for regio-,[8, 9] stereo-,[10–12] chemo- and enantioselective synthesis.[13–17] Mechanistic features, especially the evolution of the selectivity in these reactions, have been extensively studied.[18–25] Since one of the most intriguing aspects of allylpalladium chemistry is the possibility of controlling the selectivity by means of the reaction conditions and the ancillary ligands on palladium, there is currently considerable interest in investigating those electronic and steric interactions that govern the selectivity of nucleophilic attack on η^3-allylpalladium complexes.[26–31]

A recent theoretical study[29] describes a novel electronic effect which occurs between an allylic β-substituent and palladium in η^3-allylpalladium complexes. It has been shown that strong β-substituent effects induce an asymmetric electron distribution in the allylic fragment, which enhances the regioselecivity of nucleophilic attack, and increases the chemoselectivity in nucleopilic addition to conjugated dienes. This theoretical work initialised the present study, which also includes the first systematic experimental investigation of the β-substituent effect in η^3-allylpalladium complexes.

Since the β-substituent effects are particularly strong for polar β-substituents of η^3-allylpalladium complexes with *anti* configuration,[29] the investigations focused on the 4-methoxy-substituted cyclic species **1**–**4** (Scheme 1), while complex **5** represents a reference system in which the η^3-allyl moiety is in a *syn* configuration.[32] Since the β-substituent effects have strict stereoelectronic requirements, the hindered rotation at the C3–C4 bond in cyclic systems **1**–**4** allows the investigation of the angular dependence of the interactions between the β-methoxy functionality and the palladium atom. Reactions of **1**–**5** with nucleophiles have been investigated in a number of previous studies.[22, 33–35] In particular, cyclohexyl- and cycloheptylallylpalladium complexes, such as **1**, **2** and **4**, frequently occur as intermediates in synthetically useful transformations.[14, 36–38] Previous synthetic and mechanistic studies show that the regio- and chemoselectivity of nucleophilic attack are

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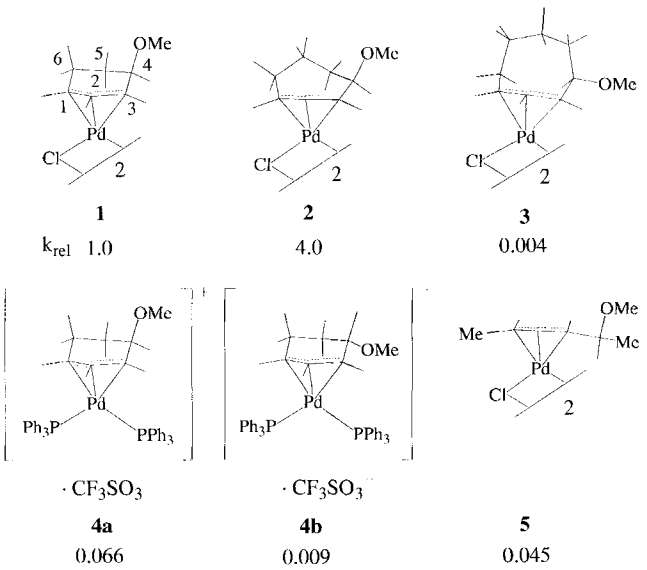
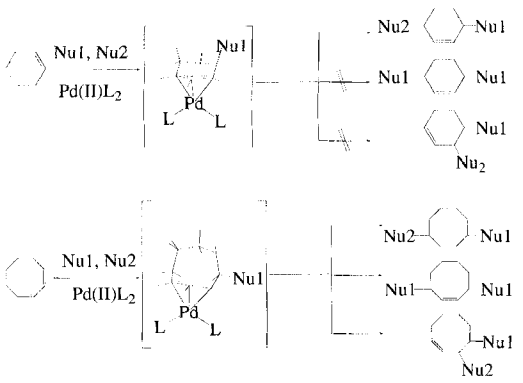


Scheme 1. η^3-Allylpalladium complexes examined in this study (k_{rel}, given below the respective compound numbers, is relative rate of deuteromethanolysis).

very high when the reaction proceeds via a cyclohexyl- or cycloheptylallylpalladium intermediate possessing a polar *trans* β-substituent (such as in **1**, **2**, **4a**).[35–37, 39] However, in the case of a cyclooctylallyl or certain acyclic intermediates the regioselectivity and sometimes the chemoselectivity is unexpectedly lower (Scheme 2).[36, 37, 39] A similar decrease in regioselectivity was observed for analogues of **4b**, in which the polar β-substituent is in a *cis* position relative to palladium.[22]



Scheme 2. Regio- and chemoselectivities of nucleophilic attack at cyclohexylallyl and cyclooctylallyl palladium intermediates.

Although the degree of regio- and chemoselectivity of nucleophilic attack implicitly depends on the strength of the β-substituent effect, a quantitative characterisation of the interactions requires the examination of a property arising directly from the β-substituent effect. An example is the weakening of the C(allyl)–X bond[29] in β-X-substituted η^3-allylpalladium complexes. Accordingly, in this study the C–O bond strength in **1**–**5** is analysed as a function of the conformation and configuration of the complexes as well as of the nature of the ancillary ligand on palladium. The experimental studies are combined with theoretical calculations in order to discuss the following questions:

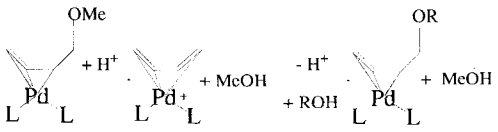
1) Which conformation and configuration of the allylic moiety provide the strongest β-substituent effects?
2) How do steric effects and hindered rotation at the C3–C4 bond change the conformation of the β-substituted allyl fragments?
3) How do electronic and steric effects of the ancillary ligands influence the strength of the β-substituent effect?
4) What predictions can be made for the chemoselectivity as a function of nucleophiles and substrates for the oxidation of conjugated dienes (cf. Scheme 2)?
5) What is the relationship between the regiochemistry of nucleophilic attack and the structure of the allylic substrate?

To answer these questions, kinetic studies were carried out for allylpalladium complexes **1**–**5**. The experimental results are interpreted by means of theoretical calculations for the corresponding model systems **6**–**10** and simplified β-substituted allyl complexes **11**–**14**. With this approach reliable predictions could be provided for the regio- and chemoselectivity of synthetically interesting transformations, since allylpalladium complexes **1**–**5** and their closely related analogues are actual intermediates in allylic substitutions and oxidation of dienes.[36–38, 40–44]

Experimental Results

Detection of the β-substituent effects is not a trivial problem, since these effects decrease the kinetic stability of the η^3-allylpalladium complexes,[29] hindering direct experimental investigation. For example, preparation of cyclic β-chloro-substituted species has not been reported yet, probably because of their low kinetic stability. Therefore, the scope of an experimental study is restricted to η^3-allylpalladium complexes with moderately strong β-substituent effects, such as the relatively stable β-methoxy-substituted species **1**–**5**.

It is well established that acid-catalysed alcoholysis of β-methoxy-substituted η^3-allylpalladium complexes takes place with cleavage of the C4–O bond (Scheme 3).[45, 46] This reaction can be carried out under mild conditions, since the palladium atom lends anchimeric assistance to the bond-breaking process.[45] This anchimeric assistance is a manifestation of the β-substituent effect,[29] which weakens the C4–O bond and, therefore, facilitates its cleavage. Hence, the rate of alcoholysis will depend on the magnitude of the anchimeric assistance, and, accordingly on the strength of the β-substituent effect.



Scheme 3. Alcoholysis of β-methoxy-substituted η^3-allylpalladium complexes.

For practical reasons deuteromethanol ($R = CD_3$ in Scheme 3) was used as the alcohol component in the kinetic measurements. Thus, the progress of the reaction could be conveniently followed by monitoring the OCH_3 signal of **1**–**5** by ^{1}H NMR spectroscopy. Deuteromethanolysis was carried out

with a > 200-fold excess of CD_3OD to ensure pseudo-first-order conditions. The reaction conditions, such as the acid (D_2SO_4) concentration and temperature (25.0 °C), were optimized to give measurable rates for all species under the same conditions (see the Experimental Section).

The observed rates of deuteromethanolysis span three orders of magnitude (Scheme 1, Figure 1). The reaction was fastest for the cycloheptylallyl complex **2**, followed by the cyclohexylallyl

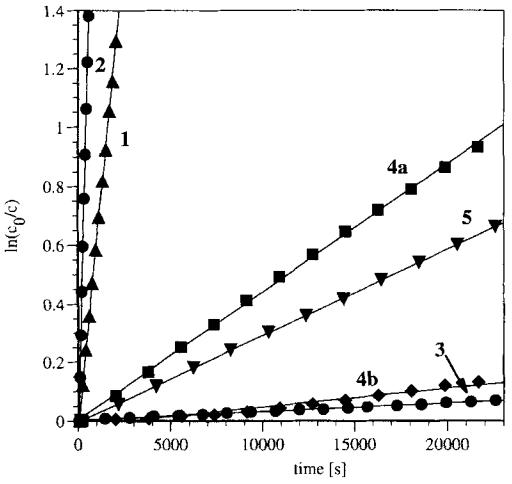


Figure 1. Plot of $\ln(c_0/c)$ against t for deuteromethanolysis of β-methoxy-substituted η^3-allylpalladium complexes **1**–**5** under the same reaction conditions. The relative rates are given in Scheme 1, and k_{obs} values and the reaction conditions in the Experimental Section.

complex **1**. Interestingly, expansion of the seven-membered ring by a single methylene unit leads to a drastic change in the rate of reaction. Deuteromethanolysis of the cycloheptylallyl complex **2** proceeds about 1000 times faster than for the cyclooctylallyl complex **3**. This remarkable decrease in the reaction rate indicates a conformationally induced weakening of the β-substituent effect in **3**. When the σ-donor chloro ligands of **1** are replaced by π-acceptor triphenylphosphine ligands (**4a**) the reaction rate decreases significantly. Furthermore, when ligand exchange is accompanied by a change of the *trans* configuration of the methoxy group to a *cis* configuration (**4b**), the reaction rate is reduced by more than two orders of magnitude. In **5** the methoxy group is attached to a secondary carbon atom (C4), as in the cyclic complexes **1**–**4**. However, in **5** the allylic functionality has a *syn* configuration,[32] and free rotation about the C3–C4 bond is possible. Because of these differences, the cyclohexylallyl complex **1** reacts more than 20 times faster than **5**.

In summary, the experimental results show that the reaction rates are decreased by 1) substantial changes in the ring conformation, 2) replacement of the σ-donor ligands by π-acceptors and 3) changing the *anti* configuration of the substituent to a *syn* configuration.

Theoretical Results and Discussion

Computational Methods: The geometries of **6**–**14** were optimized by employing a Beck[47] type three-parameter density functional model B3PW91. This so-called hybrid functional includes the exact (Hartree–Fock) exchange based on Kohn–Sham orbitals,[48] as well as the gradient-corrected exchange functional of Becke[49] and the more recent correlation functional of Perdew and Wang.[50] All calculations were carried out by using a double-ζ(DZ)+P basis set constructed from the LANL2DZ basis,[51–53] which includes relativistic effective core potentials for palladium, by adding one set of d polarization functions to the heavy atoms and a diffuse d function to palladium.[54, 55] The charges were calculated by the Natural Bond Orbital (NBO) analysis of Wienhold and co-workers.[56, 57] The theoretical calculations were performed by using the Gaussian 94 program package.[58]

The B3PW91/LANL2DZ+P geometrical parameters, C–O force constants[59] and NBO charges on the methoxy group of **6**–**14** calculated in this work are given in Figures 2–4. Structures **6**–**10** are derived from the corresponding experimentally investigated η^3-allylpalladium species **1**–**5**. Thus, the calculations were performed for monomers **6**–**8** and **10** instead of the dimeric chloro complexes **1**–**3** and **5**. This is not a serious simplification, since it has been shown that the structures and properties of monomeric and chloro-bridged η^3-allylpalladium complexes are very similar.[60, 61] The triphenylphosphine complexes **4** were approximated by the phosphine complexes **9**. Since phosphine is a fairly strong π-acceptor but a less effective σ-donor than the usual alkyl- or arylphosphines,[62–64] approximation of PPh_3 with PH_3 may lead to an underestimation of the σ-donor properties of the ancillary ligand in **9**. The C–O bond strengths are characterised by their stretching force constants k_{C-O}, which correlate well with the strength of the β-substituent effect.[29] However, it should also be noted that the dissociation energy of the C–O bonds is only indirectly related to the k_{C-O} values.

Effects of the Substituent Conformation: The rotational potential of **11a** as a function of the Pd-C3-C4-O dihedral angle τ is shown in Figure 5. This potential shows a deep minimum at 173° in the region of $120 < \tau < 300°$, which is conceivable for the β-methoxy substituents in cyclic systems. The C4–O bond strength is also a function of τ (Figure 6): this bond is weakest around 173° and strongest at 270° (−90°). As has been shown,[29] variation of the C4–O bond strength on changing τ is a characteristic feature of the β-substituent effect. In antiperiplanar conformation, such as in **11a**, the palladium–allyl bonding orbital (d_π) and a lone-pair orbital of palladium (n_d) are properly positioned for interaction with the σ*(C–O) orbital of the β-substituent (Scheme 4). Charge transfer from the occupied d_π and n_d orbitals to the antibonding σ*(C–O) orbital leads to weakening of the C–O bond. In **11b** ($\tau = -90°$), however, d_π, n_d and σ*(C–O) are orthogonal (Scheme 4) and the conjugative interactions are shut off, which strengthens the C–O bond (Figure 3).[65]

The curves in Figures 5 and 6 potentials are very similar to those obtained for the chloro-substituted species;[29] this indicates that the conjugative interactions in β-methoxy- and β-chloroallylpalladium complexes have the same character. It should also be noted that the MP2 and B3PW91 geometries (Figure 3) of **11a** and **11b** are very similar, and that the MP4SDQ relative energy of **11a** (6.7 kcal mol^{-1}) is very close to the corresponding B3PW91 value (6.1 kcal mol^{-1}). This

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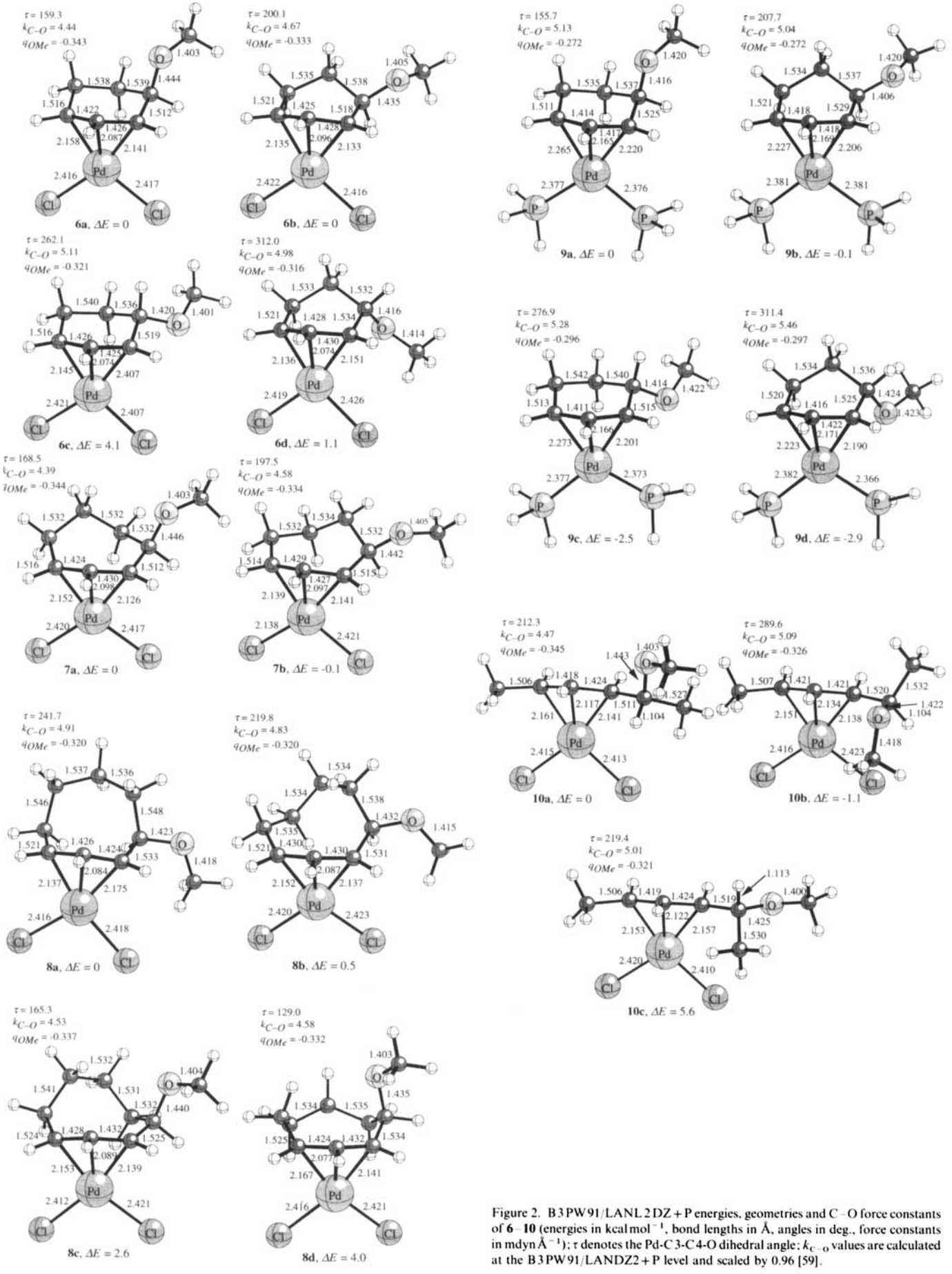


Figure 2. B3PW91/LANL2DZ+P energies, geometries and C–O force constants of **6**–**10** (energies in kcal mol^{-1}, bond lengths in Å, angles in deg., force constants in mdyn Å^{-1}); τ denotes the Pd-C3-C4-O dihedral angle; k_{C-O} values are calculated at the B3PW91/LANDZ2+P level and scaled by 0.96 [59].

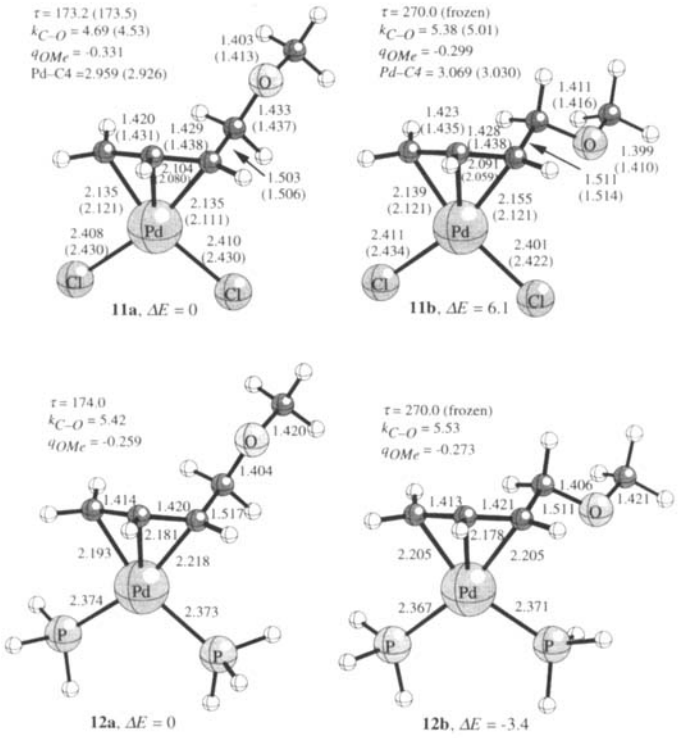


Figure 3. Structures of model systems **11**–**12** (for computational details see the caption for Figure 2). The MP2 geometrical parameters [29] are given in paranthesis.

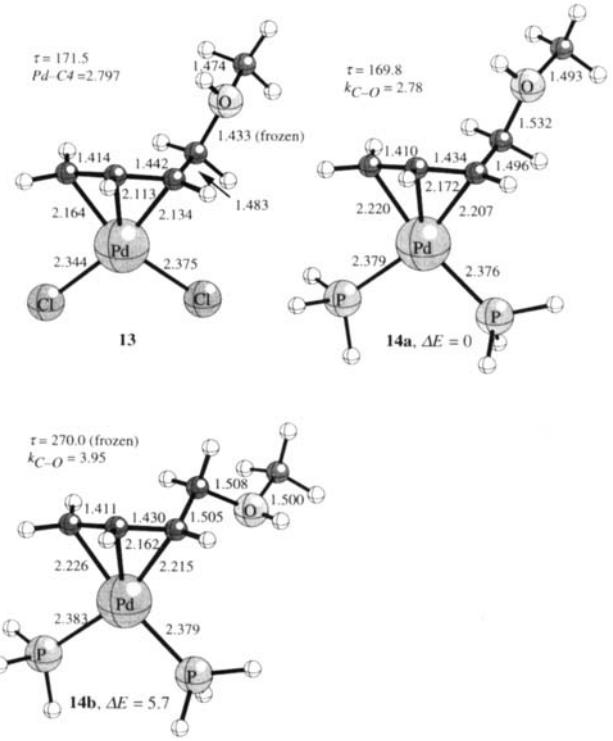


Figure 4. Protonated model systems **13**–**14**. (for computational details see the caption for Figure 2).

agreement is, however, not surprising, since it has been shown that the hybrid functional methods perform very well for second-row transition metals and closely approach the accuracy of the advanced ab initio methods, such as MP2–4, QCISD and CCSD.[66–68]

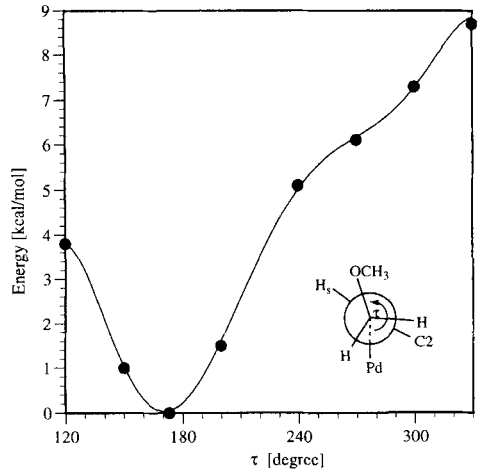


Figure 5. Rotation potential of **11a**. Energy values are obtained by freezing the Pd-C3-C4-O dihedral angle τ to different values and reoptimizing all other geometrical parameters at the B3PW91/LANL2DZ+P level.

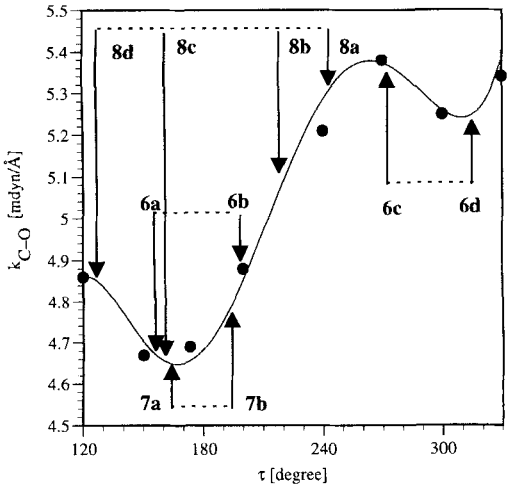
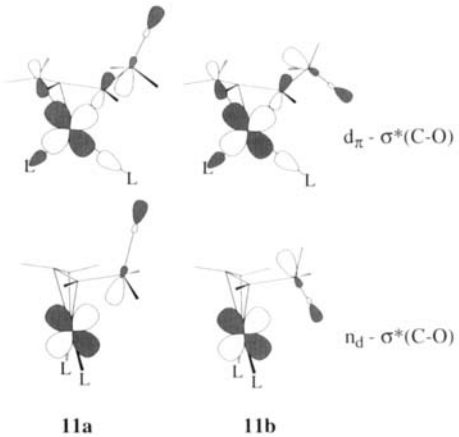


Figure 6. Stretching force constant k_{C-O} of **11a** as a function of τ. The τ dihedral angles of the corresponding cyclic complexes are indicated by arrows.



Scheme 4. Interactions of the palladium–allyl bonding orbital (d_π) and a lone-pair orbital of palladium (n_d) with the σ*(C–O) orbital in **11a** and **11b**.

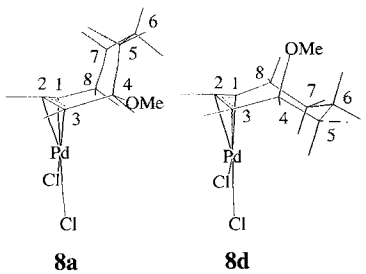
Effects of the Ring Conformation: Because of the allyl–metal interactions[30, 69] the C1–C4 fragment is confined to a rigid conformation in **6**–**8**, which considerably reduces the ring flexibility and the number of possible conformers.

0947-6539/97/0304-0596 $ 17.50+.50/0 Chem. Eur. J. 1997, 3, No. 4

Six-Membered Ring: In accordance with the previous X-ray studies on cyclohexylallyl complexes,[70] two conformers were found for the *trans*-methoxy-substituted species, namely, **6a** and **6b**. These have the same energy (Figure 2), and hence the two forms are equally populated at room temperature. In **6a** and **6b** the methoxy functionalities are biased towards conformations which are favoured by the β-substituent effect. In **6a** τ (159°) deviates by only 14° from the optimal value for conjugative interactions (173°, **11a**), and, accordingly, the C–O bond is considerably weakened and lengthened. Weakening of the C–O bond is also reflected by its low stretching force constant in **6a** (4.44 mdyn Å^{-1}), which is 20% smaller than the C–O force constant in dimethyl ether (k_{C-O} = 5.54 mdyn Å^{-1}, B3PW91/LANL2DZ+P). This also explains the rapid replacement of the OCH_3 group in the corresponding complex **1** (Scheme 1). Contrary to the *trans* substitutents in **6a** and **6b**, the *cis* substituents in **6c** and **6d** are less available for conjugative interactions, since τ in these complexes is 262 and 312°, respectively (Figure 6).

Seven-Membered Ring: Two conformers (**7a** and **7b**) were obtained for the cycloheptylallyl complex, with the same total energy, within 0.1 kcal mol^{-1}, suggesting that the two forms are about equally populated at room temperature. The geometries of **7a** and **7b** are similar to that of the X-ray structure of a cycloheptyallylpalladium analogue reported by Björkman and Bäckvall.[71] The structure of **7a** is especially interesting as here τ (169°) deviates by only 4° from the dihedral angle (173°) that is optimal for conjugative interactions. Consequently, the C–O bond is even longer and weaker in **7a** than in **6a**. Thus, the very fast deuteromethanolysis of **2** can be explained by the fact that in one of its equally populated conformers, the dihedral angle τ closely approaches the value that is optimal for the β-substituent effect, which provides powerful anchimeric assistance in the C–O bond-breaking process.

Eight-Membered Ring: Expansion of the seven-membered ring by a CH_2 unit leads to considerable changes in the ring geometry and the conformation of the β-substituent. Four forms with rather different stabilities were found for the cyclooctylallyl palladium complex (**8a–d**). The side view of the complexes in Scheme 5 shows that the two basic conformers **8a** and **8d** bear a resemblance to the boat (**6b**) and chair (**6a**) forms of the cyclohexyl complexes, respectively. The lower relative stability of **8d** arises from a nonbonding strain between the palladium atom and the *cis*-H atoms of C5 and C7, as well as from a diaxial strain between the methoxy group and *trans*-H6 and H8 atoms. Since the Pd–H5(*cis*) and Pd–H7(*cis*) distances are about 2.7 Å, which is considerably shorter than the sum of the van der Waals radii[72, 73] of the palladium and hydrogen atoms (3.5 Å), the repulsive interactions between the metal atom and *cis*-H atoms are quite strong in **8d**. In intermediate structures **8b** and **8c** this strain is partially relieved, but the diaxial strain is retained in **8b** and even increased in **8c**, so that **8c** is less stable than **8a** and **8b**. Conformer **8a** is the most stable, and, accordingly the most highly populated form. The dihedral angle τ is 242° in **8a**, which deviates by 69° from the value (173°) that is optimal for β-substituent effects (Figure 6). Consequently, the C–O bond in **8a** is stronger than the C–O bond in any other *trans*-β-substituted cyclic chloro complexes. In contrast to **8a**, the conformation of the methoxy group (τ = 165.3°) in **8c** is favoured by the β-substituent effect; however, this conformer is thermodynamically much less stable than the **8a** and **8b** forms.



8a **8d**

Scheme 5. Side views of the conformers **8a** and **8d**.

Since the β-substituent effects are weak in the thermodynamically stable conformers **8a** and **8b**, the anchimeric assistance to cleavage of the C4–O bond is also rather weak. To enhance the conjugative interactions between Pd and C4–O, **8a** and **8b** have to be converted to the **8c** form before C–O bond cleavage takes place. Accordingly, the deuteromethanolysis of **3** is much slower than that of **1** and **2** (Figure 1), in which strong β-substituent interactions are present even in the thermodynamically most stable conformers (**6a,b** and **7a,b**).

Apparently, variation of the strength of the β-substituent effect in **6**, **7** and **8** is a result of the simultaneous action of steric and stereoelectronic effects. Such conformationally induced or inhibited stereoelectronic effects are of great importance in determining the selectivity in allylpalladium chemistry.

Ligand Effects: Since π-acceptor phosphine ligands are often used to activate η^3-allylpalladium complexes toward nucleophilic attack,[1–3, 30] the influence of these ligands on the β-substituent effect is especially important. The *trans*-β-substituted complexes **9a** and **9b** are very close in energy. The ring geometry and the value of the dihedral angle τ in **9a** and **9b** are very similar to the corresponding parameters in the chloro complexes **6a** and **6b**. Accordingly, the change in the C–O bonding can be attributed to the markedly different electronic effects of the phosphine and chloro ligands. As one goes from **6a** to **9a** the C–O bond is shortened by 0.03 Å and k_{C-O} is increased by 15%, which indicates a considerable reduction of the β-substituent effect. Replacement of the σ-donor chloro ligand with a π-acceptor phosphine ligand results in charge transfer from the metal to PH_3 by back-donation, which leads to orbital contraction and, therefore, lowering of the n_d level (Scheme 4). Decreasing the energy of n_d causes the energy gap between n_d and σ^*(C–O) to increase, which leads to weakening of the orbital interactions.[29]

In contrast to *cis*-substituted chloro complexes **6c** and **6d**, phosphine complexes **9c** and **9d** are somewhat more stable than the *trans*-substituted analogues. This difference can be ascribed to two important effects: 1) decline of the β-substituent effect in *trans*-substituted phosphine complexes, and 2) the nonbonding strain between palladium and *cis*-H's or a *cis*-substituent is weaker in a phosphine complex than in a chloro complex, since the Pd–allyl distances are longer by 0.06–0.10 Å in a phosphine complex than in a chloro complex. The C–O bonds of the *cis*-β-substituted phosphine complexes (**9c, d**) are even stronger than those of the *trans*-β-substituted analogues (**9a, b**).

The slower deuteromethanolysis of **4a** compared to **1** can certainly be explained by the decrease in the β-substituent effect

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caused by replacement of the σ-donor chloride ligand by the π-acceptor triphenylphosphine. On the other hand, the C–O bond in **9b** is about as strong as in **8a**, and the deuteromethanolysis of the corresponding species **4a** is 15 times faster than that of **3**. This discrepancy is due to the fact that under the experimental conditions the β-substituent effect in **4** is somewhat stronger than in the corresponding model compounds **9a–d**. The PH_3 ligand is a much weaker σ-donor than the alkyl- or arylphosphines,[62–64] and, since the strength of the β-substituent effect is directly proportional to the σ-donor ability of the ancillary ligand,[29] the influence of the β-substituent effect on the structure of **4a,b** is stronger than on the structure of **9a–d**. Furthermore, protonation of the methoxy group (vide infra) amplifies the β-substituent effect in **4a** to a considerably larger extent than in **3**, since in the cyclohexylallyl complex **4a** the stereoelectronic requirements of the Pd–C4-O(Me) interactions are satisfied, even in the thermodynamically most stable conformers (**9a,b**).

Effects of Configuration and Free Rotation about the C3–C4 Bond: Three conformers were found for the acyclic complex **10**, in which the β-functionality is in a *syn* configuration. The β-substituent effect is much stronger in **10a** than in the thermodynamically more stable conformer **10b**. Thermodynamic stabilization by the β-substituent effect is about 40% lower in a *syn* than in an *anti* configuration.[29] Furthermore, the steric repulsion between the 4-Me group and Pd is stronger than between 4-OMe and Pd, and this leads to larger steric strain in **10a** than in **10b**. Accordingly, **10a** will be less populated than **10b**, and C–O bond cleavage has to be preceded by conversion of **10b** to **10a**. Therefore deuteromethanolysis of **5** is slower than that of cyclic species **1** and **2**.

The third conformer **10c** is much less stable than **10a** and **10b**, and it probably does not exist under standard conditions. However, it shows an interesting structural feature: the unusually long C4–H4 bond (1.113 Å), which can be ascribed to the conjugative interactions between the C4–H4 bond and palladium. This is also an example of the participation of a C–H bond in β-interactions,[29] and shows that methyl and alkyl groups may exert significant *electronic* effects in η^3-allylpalladium complexes.

Charge distribution: The negative charge on the methoxy group q_{OMe} is also directly proportional to the strength of the β-substituent effect (Figures 2–3). As one goes from strongly interacting cyclic complexes **6a,b** and **7a,b** to weakly interacting ones **9a–d**, the charge on the methoxy group decreases by about 0.07 electrons. Since in *trans*-β-methoxy complexes, in which τ is close to 180°, the C–O bond is parallel with the direction of the external nucleophilic attack, charge accumulation on the OMe substituent generates repulsive electrostatic interactions with the electron-rich nucleophile. These repulsive interactions are weaker when the more remote (less substituted) allylic terminus is attacked, which also increases the regioselectivity of the nucleophilic attack.

Solvent effects: Two important structural factors are expected to influence the effects of the medium on the stability of the various conformers: 1) charge accumulation on the OMe group, and 2) availability of the OMe group for the solvent molecules. In order to estimate the solvent effects on the conformational energies, solvation energy corrected relative energies (ΔE_{solv}) were calculated for selected species (**6a–d** and **8a–d**) by using the Onsager model within the self-consistent reaction field (SCRF) theory[74, 75] assuming a continuous dielectric medium of $\varepsilon = 33.6$.[76] According to the SCRF/HF/LANL2DZ+P single-point calculations[77] on the gas-phase B3PW91/LANL2DZ+P geometries, solvation slightly stabilises the *trans* complex **6a** (ΔE_{solv} = 0, 0.7, 2.6, 3.3 kcal mol^{-1} for **6a–d**), in which the OMe group bears a higher negative charge than in any other form. However, in the case of the cyclooctylallyl complexes, solvation stabilises **8a** to a larger extent than the other three conformers (ΔE_{solv} = 0, 3.4, 3.1, 4.6 kcal mol^{-1} for **8a–d**), since in **8b–d** the effective solvation of the OMe group is hindered by the close contact between the oxygen atom and the axial hydrogen atoms (vide supra).

Protonation of the Methoxy Groups: Replacement of the OCH_3 group with a OCD_3 group in **1–5** requires acid catalysis. Protonation of the oxygen atom decreases the energy of the σ*(C–O) MO, thereby amplifying the β-substituent effect. In the case of the chloro complexes the β-substituent effect become so strong that an *O*-protonated complex such as **13** decomposes without an activation barrier to (η^4-diene)palladium dichloride and MeOH, which, of course, severely hampers both the experimental and theoretical investigation of such species. Decomposition of **13** (Figure 4) is hindered by freezing the C4–O bond at 1.433 Å, which is the C4–O bond length in the unprotonated complex **11a**. Comparison of **13** and **11a** reveals some typical structural changes caused by the increased β-substituent effect: 1) shortening of the Pd–C4 bond by 0.16 Å, 2) asymmetrisation of the Pd–C_t bonds and 3) shortening of the C3–C4 bond. Nevertheless, the conformation of the complex remains practically unchanged (τ = 173° in **11a** and 172° in **13**), which shows that the antiperiplanar conformation is favoured by the β-substituent effect in both the parent and the *O*-protonated species.

In contrast to the chloro complex **13**, the *O*-protonated phosphine complex **14a** represents a minimum on the potential energy surface. While the β-substituent effects are very weak in the unprotonated form **12a**, the conjugative interactions between Pd and the β-substituent are relatively strong in **14a**. When the CH_2OMe group of **12a** is rotated to τ = 270° (**12b**) the complex is stabilised because the steric strains are relieved.[29] However, the same process destabilises the protonated species (**14a** → **14b**). Furthermore, the C–O bond in **12a** is about as strong as in **12b**, while in case of the protonated species k_{C-O} increases by 42% from **14a** (2.78 mdyn Å^{-1}) to **14b** (3.95 mdyn Å^{-1}). Similar effects will apply for the cyclic analogues **9a–d**. The protonation of the OMe group increases the β-substituent effect in **9a** and **9b** (where the conformation is favourable for conjugative interactions) to a much larger extent than in **9c** and **9d**; this explains the large difference in the reactivity of **4a** and **4b**.

Further Allylpalladium Species

Detection of the β-Substituent Effect: Since the electronic interactions between β-substituents and palladium strongly influence the regio- and chemoselectivity of synthetically important trans-

0947-6539/97/0304-0598 $ 17.50+.50/0 Chem. Eur. J. 1997, 3, No. 4

formations, quantitative information on the strength of these interactions is very useful for the development of selective palladium-catalysed preparative procedures. The above study demonstrates that measurement of the rate of deuteromethanolysis provides a simple method for determining the β-substituent effect in η^3-allylpalladium complexes. The kinetic measurements can be carried out on a standard NMR spectrometer with relatively inexpensive chemicals (10–15 mg of complex, 0.4 mL of $CDCl_3$, 0.3 mL of CD_3OD and a trace of D_2SO_4; vide infra).

Considering the previous[22, 36, 37, 39] and present results it can be concluded that if the rate of deuteromethanolysis (under the described experimental conditions) is as slow or slower than the rate obtained for **3** and **4b**, the β-substituent effects are so weak that they are not able to control the regioselectivity of nucleophilic attack (cf. Scheme 2, bottom). Reaction rates much slower than those obtained for **3** or **4b** can be measured by adding more D_2SO_4 to the reaction mixture, but, in this case, the new system has to be calibrated by means of one of the investigated complexes (e.g. **3**). However, often a simple qualitative result, such as a very slow rate, can be informative in itself.

The experimental detection of the β-substituent effect can be easily extended to other allylpalladium complexes with alkoxyl, hydroxyl, or acetoxyl groups with only a slight variation of the reaction conditions.

Chemoselectivity in 1,4-oxidation of Conjugated Dienes: Bäckvall and co-workers have shown that for certain nucleophile combinations, the 1,4-oxidation of conjugated dienes can be carried out with high chemoselectivity.[36, 39] Accordingly, starting from a symmetrical diene and two different nucleophiles (e.g., $Nu1^- = OAc^-$, $Nu2^- = Cl^-$) one of the three possible products is formed selectively (Scheme 2, top). This type of selectivity can be explained by variation of the strength of the β-effect with the substituent (Nu1 or Nu2) in the η^3-allylpalladium intermediate. A substituent engaged in a strong conjugative interaction with palladium (e.g. Nu1 = Cl) generates a complex that is kinetically unstable because of a weak C4–Nu bond. This complex decomposes before attack by another nucleophile takes place. However, when the C4–Nu bond is relatively strong, because of a weakening of the β-substituent effect (e.g. Nu1 = OAc), the η^3-allylpalladium intermediate will be stable, and it will be attacked by the available stronger nucleophile.

This study provides an analysis of the β-substituent effect in realistic allylpalladium complexes and, therefore, can help to find new nucleophile pairs that are suitable for a chemoselective 1,4-oxidation reaction. A high chemoselectivity is expected under the following reaction conditions:

1) Cyclohexadiene or cycloheptadiene derivatives are used as the diene component, since the β-substituent conformation in these complexes is strongly favoured by the conjugative interactions.
2) The weaker nucleophile is able to form a less polar C4–Nu bond to provide a kinetically stable η^3-allylpalladium intermediate.
3) Proton catalysis can be applied to amplify the β-substituent effect, and, accordingly, to increase the difference in the kinetic stability of the η^3-allylpalladium intermediates.

Regioselectivity of Nucleophilic Attack: It was shown above that steric interactions which displace the Pd–C3 and C4–O bonds from an antiperiplanar conformation considerably decrease the strength of the β-substituent effect. For less polar β-substituents, such as hydrogen and alkyl groups[29] (cf. **10c**), small deviations from the favoured antiperiplanar conformation can completely eliminate the β-substituent effect, which can lead to lowering of the regiopreference of the nucleophilic attack. This effect can be a very important factor for the regioselectivity in asymmetric catalysis, where very often only weakly conjugating β-alkyl substituents are present in the allylpalladium intermediates. The synthetic value of such a catalytic transformation is equally dependent on the degree of the enantio- and regioselectivity. However, high enantioselectivity can be accompanied by poor regioselectivity.[14, 78] According to Consiglio and Waymouth,[15] "One of the more severe limitations hindering further development of (enantioselective) allylic substitution reactions is regiocontrol in the nucleophilic attack". The asymmetric induction is usually provided by a bulky chiral ligand on palladium, which is also allowed to interact with the allylic β-substituents. However, when the β-substituent is displaced from the antiperiplanar geometry, the β-substituent effect, and thus also the regioselectivity, will considerably decrease. Analogous sterically and conformationally induced reductions in the β-substituent effect are discussed for **8a** and **10b**. Clearly, steric interactions with conjugated β-substituents have to be carefully considered in the design of chiral ligands if a high degree of regioselectivity is also desired.

Conclusions

This study provides the first example of a systematic experimental investigation of the β-substituent effect in η^3-allylpalladium complexes. The experimental method, which is based on the deuteromethanolysis of β-methoxy-substituted complexes, is simple and inexpensive, and with slight modification it could be applied to a wide range of η^3-allylpalladium complexes. By measurement of the strength of the β-substituent effect, reliable predictions can be made for the regio- and chemoselectivity of nucleophilic attack in allylic substitution and 1,4-oxidation of conjugated dienes.

The theoretical studies have shown that a six- and a seven-membered ring framework provide a *trans*-β-substituent conformation (**6a, b** and **7a, b**) that is particularly favoured by the β-substituent effect. On the other hand, in the thermodynamically stable forms of the cyclooctylallyl complex (**8a, b**) the *trans*-β-substituent conformation is not optimal for conjugative interactions, and this leads to a weaker β-substituent effect. Similarly, the *cis*-β-substituent geometry (**6c, d** and **9c, d**) and an acyclic framework (**10a, b**) are typical structural factors which lead to weakening of the interactions between a polar β-substituent and palladium. Ancillary ligands with a pronounced π-acceptor character also reduce the strength of the interactions, even in cases where the stereoelectronic requirements of the β-substituent effect are satisfied (**9a, b**). Protonation of the methoxy substituent can dramatically increase the strength of the β-substituent effect, regardless of the σ-donor and π-acceptor nature of the ancillary ligands.

Experimental Section

The preparation and characterization of complexes **1**–**5** is given in the literature.[22, 32, 34, 35, 45, 79] All complexes were carefully purified by chromathography or recrystallization. The *cis* and *trans* isomers of the triphenylphosphine complexes **4a** and **4b** could not be separated; therefore, the isomer mixture was used in the kinetic measurements. The reactions were studied on a Varian Unity 400 NMR spectrometer operating at 400 MHz for ^{1}H NMR spectra. The appropriate complex (0.02 mmol) was dissolved in a mixture of $CDCl_3$ (0.4 mL) and CD_3OD (0.2 mL) in an NMR tube. To this mixture 0.100 mL of stock solution was added by syringe. The stock solution was prepared from CD_3OD (5 mL) and 98% D_2SO_4 in D_2O (0.092 g). At appropriate intervals ^{1}H NMR spectra were recorded in arrayed-experiment mode at 25.0 °C. The k_{obs} values for the disappearance of the substrates were calculated from integrals of the OCH_3 peaks versus time by means of regression analysis. The measured absolute k_{obs} values are: 6.61×10^{-4} (**1**), 2.63×10^{-3} (**2**), 2.97×10^{-6} (**3**), 4.40×10^{-5} (**4a**), 5.77×10^{-6} (**4b**), $2.99 \times 10^{-5}\ s^{-1}$ (**5**).

Acknowledgements: This work was supported by the Swedish Natural Science Research Council (NFR). The calculations were performed on the IBM SP2 parallel computer facility of the Parallelldatorcentrum (PDC), Stockholm, Sweden. The author thanks the PDC for a generous allotment of computer time.

Received: October 15, 1996 [F497]

[1] J. Tsuji, *Palladium Reagents and Catalysis: Innovations in Organic Synthesis*, Wiley, Chichester, **1995**, Chapts. 3 and 4.
[2] J. A. Davies, in *Comprehensive Organometallic Chemistry II*; *Vol.9* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson and R. J. Puddephatt), Elsevier, New York, **1995**, Chapt. 6.
[3] S. A. Godleski, in *Comprehensive Organic Synthesis*; *Vol. 4* (Eds.: B. M. Trost and I. Flemming), Pergamon Press, New York, **1991**, Chapt. 3.3.
[4] J. Tsuji, *Tetrahedron* **1986**, *42*, 4361.
[5] B. M. Trost, *Acc. Chem. Res.* **1980**, *13*, 385.
[6] L. S. Hegedus, *Transition Metals in the Synthesis of Complex Organic Molecules*, University Science Books, Mill Valley, California, **1994**.
[7] J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, Oxford University Press, Mill Valley, California, **1987**.
[8] J.-E. Bäckvall, *Pure Appl. Chem.* **1992**, *64*, 429.
[9] J.-E. Bäckvall, *Acc. Chem. Res.* **1983**, *16*, 335.
[10] J.-E. Bäckvall, *Organometallic Reagents in Organic Synthesis*, Academic Press, London, **1994**, p. 81.
[11] A. Heumann, M. Réglier, *Tetrahedron* **1995**, *51*, 975.
[12] J.-E. Bäckvall, *Adv. Met. Org. Chem.* **1989**, *1*, 135.
[13] B. M. Trost, D. L. V. Vranken, *Chem. Rev.* **1996**, *96*, 395.
[14] B. M. Trost, *Acc. Chem. Res.* **1996**, *29*, 355.
[15] G. Consiglio, R. W. Waymouth, *Chem. Rev.* **1989**, *89*, 257.
[16] A. Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339.
[17] C. G. Frost, J. Howarth, J. M. J. Williams, *Tetrahedron: Asymmetry* **1992**, *3*, 1089.
[18] J.-E. Bäckvall, K. L. Granberg, A. Heumann, *Isr. J. Chem.* **1991**, *31*, 17.
[19] B. Åkermark, S. Hansson, B. Krakenberger, A. Vitagliano, K. Zetterberg, *Organometallics* **1984**, *3*, 679.
[20] B. Åkermark, K. Zetterberg, S. Hansson, B. Krakenberger, A. Vitagliano, *J. Organomet. Chem.* **1987**, *335*, 133.
[21] B. Crociani, S. Antonaroli, F. D. Bianca, L. Canovese, F. Visentin, P. Uguagliati, *J. Chem. Soc. Dalton Trans.* **1994**, 1145.
[22] J.-E. Bäckvall, R. E. Nordberg, K. Zetterberg, B. Åkermark, *Organometallics* **1983**, *2*, 1625.
[23] P. v. Matt, G. C. Lloyd-Jones, A. B. E. Minidis, A. Pfaltz, L. Macko, M. Neuburger, M. Zehnder, H. Rüegger, P. S. Pregosin, *Helv. Chim. Acta* **1995**, *78*, 265.
[24] P. R. Auburn, P. B. Mackenzie, B. Bosnich, *J. Am. Chem. Soc.* **1985**, *107*, 2033.
[25] P. B. Mackenzie, J. Whelan, B. Bosnich, *J. Am. Chem. Soc.* **1985**, *107*, 2046.
[26] B. Åkermark, J. D. Oslob, P.-O. Norrby, *Organometallics* **1995**, *14*, 1688.
[27] E. Peña-Cabrera, P.-O. Norrby, M. Sjögren, A. Vitagliano, V. D. Felice, J. Oslob, S. Ishii, D. O'Neill, B. Åkermark, P. Helquist, *J. Am. Chem. Soc.* **1996**, *118*, 4299.
[28] A. M. Castaño, A. Aranyos, K. J. Szabó, J.-E. Bäckvall, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2551.
[29] K. J. Szabó, *J. Am. Chem. Soc.* **1996**, *118*, 7818.
[30] K. J. Szabó, *Organometallics* **1996**, *15*, 1128.
[31] S. Sakaki, H. Satoh, H. Shono, Y. Ujino, *Organometallics* **1996**, *15*, 1713.
[32] A. Gogoll, J. Gomes, M. Bergkvist, H. Grennberg, *Organometallics* **1995**, *14*, 1354.
[33] B. M. Trost, T. R. Verhoeven, *J. Am. Chem. Soc.* **1979**, *101*, 1595.
[34] K. L. Granberg, J.-E. Bäckvall, *J. Am. Chem. Soc.* **1992**, *114*, 6858.
[35] J.-E. Bäckvall, R. E. Nordberg, D. Wilhelm, *J. Am. Chem. Soc.* **1985**, *107*, 6892.
[36] J.-E. Bäckvall, J.-E. Nyström, R. E. Nordberg, *J. Am. Chem. Soc.* **1985**, *107*, 3676.
[37] J. E. Bäckvall, S. E. Byström, R. E. Nordberg, *J. Org. Chem.* **1984**, *49*, 4619.
[38] J.-E. Bäckvall, J. O. Vågberg, *J. Org. Chem.* **1988**, *53*, 5695.
[39] J.-E. Bäckvall, J. Vågberg, R. E. Nordberg, *Tetrahedron Lett.* **1984**, *25*, 2717.
[40] J.-E. Bäckvall, K. L. Granberg, P. G. Andersson, R. Gatti, A. Gogoll, *J. Org. Chem.* **1993**, *58*, 5445.
[41] D. R. Deardorff, R. G. Linde, A. M. Martin, M. J. Shulman, *J. Org. Chem.* **1989**, *54*, 2759.
[42] R. S. Valpey, D. J. Miller, J. M. Estes, S. A. Godleski, *J. Org. Chem.* **1982**, *47*, 4717.
[43] P. S. Manchand, H. S. Wong, J. F. Blount, *J. Org. Chem.* **1978**, *43*, 4769.
[44] J. Tsuji, H. Kataoka, Y. Kobayashi, *Tetrahedron Lett.* **1981**, *22*, 2575.
[45] S. D. Robinson, B. L. Shaw, *J. Chem. Soc.* **1963**, 4806.
[46] Y. I. M. Nilsson, A. Aranyos, P. G. Andersson, J.-E. Bäckvall, J.-L. Parrain, C. Ploteau, J.-P. Quintard, *J. Org. Chem.* **1996**, *61*, 1825.
[47] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.
[48] W. Kohn, L. J. Sham, *Phys. Rev.* **1965**, *140*, 1133.
[49] A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098.
[50] J. P. Perdew, Y. Wang, *Phys. Rev. B* **1992**, *45*, 13244.
[51] T. H. Dunning, P. J. Hay, *Modern Theoretical Chemistry*, Plenum, New York, **1977**, p. 1.
[52] P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 270.
[53] P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299.
[54] S. Huzinaga, J. Andzelm, M. Klobukowski, E. Radzio-Andzelm, Y. Sakai, H. Tatewaki, *Gaussian Basis Sets for Molecular Calculations*, Elsevier, Amsterdam, **1984**.
[55] Exponents for the d functions: C, 0.630; O, 1.154; P, 0.340; Cl, 0.514; Pd (diffuse d function), 0.0628.
[56] A. E. Reed, R. B. Weinstock, F. Weinhold, *J. Chem. Phys.* **1985**, *83*, 735.
[57] A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *1988*, 899.
[58] M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheesman, T. A. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzales, J. A. Pople, *Gaussian 94*, Gaussian Inc., Pittsburgh, PA, **1995**.
[59] M. W. Wong, *Chem. Phys. Lett.* **1996**, *256*, 391.
[60] R. J. Goodfellow, L. M. Venazi, *J. Chem. Soc. (A)* **1966**, 784.
[61] L. S. Hegedus, B. Åkermark, D. J. Olsen, O. P. Anderson, K. Zetterberg, *J. Am. Chem. Soc.* **1982**, *104*, 697.
[62] S.-X. Xiao, W. C. Trogler, D. E. Ellis, Z. Berkovitch-Yellin, *J. Am. Chem. Soc.* **1983**, *105*, 7033.
[63] D. S. Marynick, *J. Am. Chem. Soc.* **1984**, *106*, 4064.
[64] C. A. Tolman, *J. Am. Chem. Soc.* **1970**, *92*, 2953.
[65] T. A. Albright, J. K. Burdett, M.-H. Whangbo, *Orbital Interactions in Chemistry*, Wiley, New York, **1985**, Chapts. 7,10 and 11.
[66] P. E. Siegbahn, in *Advances in Chemical Physics*; *Vol.43* (Eds.: I. Prigogine and S. A. Rice), Wiley, New York, **1996**, pp. 333.
[67] V. Barone, C. Adamo, *J. Phys. Chem.* **1996**, *100*, 2094.
[68] F. D. Proft, J. M. L. Martin, P. Geerlings, *Chem. Phys. Lett.* **1996**, *256*, 400.
[69] R. Goddard, C. Krüger, F. Mark, R. Stansfield, X. Zhang, *Organometallics* **1985**, *4*, 285.
[70] H. Grennberg, V. Langer, J.-E. Bäckvall, *J. Chem. Soc. Chem. Commun.* **1991**, 1190.
[71] E. E. Björkman, J.-E. Bäckvall, *Acta Chem. Scand.* **1983**, *A 37*, 503.
[72] P.-O. Norrby, B. Åkermark, F. Hæffner, S. Hansson, M. Blomberg, *J. Am. Chem. Soc.* **1993**, *115*, 4859.
[73] A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441.
[74] M. W. Wong, M. J. Frisch, K. B. Wiberg, *J. Am. Chem. Soc.* **1991**, *113*, 4776.
[75] M. W. Wong, K. B. Wiberg, M. J. Frisch, *J. Am. Chem. Soc.* **1992**, *114*, 523.
[76] J. W. Moore, R. G. Pearson, *Kinetics and Mechanism*, Wiley, New York, **1981**, p. 234.
[77] Employment of the B3PW91 hybrid functional in the SCRF calculations leads to severe convergence problems. The radii of the spherical solvent cavities are calculated from the gas-phase molecular volume of the complexes.
[78] B. M. Trost, A. C. Krueger, R. C. Bunt, J. Zambrano, *J. Am. Chem. Soc.* **1996**, *118*, 6520.
[79] S. D. Robinson, B. L. Shaw, *J. Chem. Soc.* **1964**, 5002.

0947-6539/97/0304-0600 $ 17.50+.50/0