Origin of the Regio- and Stereoselectivity in Palladium-Catalyzed Electrophilic Substitution via Bis(allyl)palladium Complexes

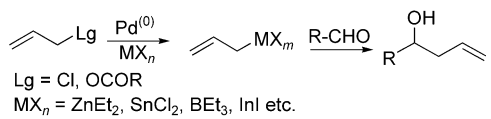
Olov A. Wallner and Kálmán J. Szabó*[a]

Abstract: Palladium-catalyzed allylic substitution of aryl allyl chlorides with aromatic and heteroaromatic aldehydes was performed in the presence of hexamethylditin. This procedure involves palladium-catalyzed formation of transient allylstannanes followed by generation of a bis(allyl)palladium intermediate, which subsequently reacts with the aldehyde electrophile. The catalytic substitution reaction proceeds with high regio- and stereoselectivity. The stereoselectivity is affected by the steric and electronic properties of the allylic substituents. Various functionalities including NO_2, $COCH_3$, Br, and F groups are tolerated under the applied catalytic conditions. Density functional calculations at the B3PW91/DZ+P level of theory were applied to study the steric and electronic effects controlling the regio- and stereoselectivity of the electrophilic addition. The development of the selectivity was studied by modeling the various bis(allyl)palladium species occurring in the palladium-catalyzed substitution of cinnamyl chloride with benzaldehyde. It was found that the electrophilic attack proceeds via a six-membered cyclic transition state, which has a pronounced chair conformation. The regioselectivity of the reaction is controlled by the location of the phenyl group on the η^1-allyl moiety of the complex. The stereoselectivity of the addition process is determined by the relative configuration of the phenyl substituents across the developing carbon–carbon bond. The lowest energy path corresponds to the formation of the branched allylic isomer with the phenyl groups in *anti* configuration, which is in excellent agreement with the experimental findings.

Keywords: allyl ligands · density functional calculations · electrophiles · palladium · regioselectivity · stereoselectivity

Introduction

Employment of palladium catalysis to generate reactive allylmetal intermediates from allyl chlorides and acetates offers a powerful approach for stereo- and regioselective transformation of electrophilic substrates.[1] There are two basically different methods to perform these reactions. The first one involves palladium-catalyzed formation of allylmetal species that are reactive enough to couple directly with the electrophiles (Scheme 1).[2–9] Recently, we have published[10, 11] another method for palladium-catalyzed allylic substitution which involves formation of transient allylstannane reagents generated from allyl chloride or acetate precursors (Scheme 2) in the presence of hexamethylditin. In this reaction the allylstannane intermediate is not reactive enough for direct addition to the electrophile, but it undergoes transmetalation with the monoallylpalladium complex available in the reaction mixture to generate a bis(allyl)palladium complex.[12, 13] Subsequently, the bis(allyl)palladium intermediate reacts[13–18] with various electrophiles such as aldehydes, imines, and activated alkenes.



Scheme 1. Palladium-catalyzed formation of reactive allylmetal intermediates followed by direct addition to electrophiles.

We have found that the palladium-catalyzed electrophilic substitution reaction (Scheme 2) proceeds with an excellent regioselectivity to yield the branched allylic product. Interestingly, this regiochemistry is in sharp contrast with the regioselectivity of the nucleophilic attack on (η^3-allyl)palladium complexes, which usually takes place at the less substituted allylic terminus.[19–23] The stereoselectivity of the reaction is dependent on the actual allyl precursor and electrophile combination. A very high level of stereoselectivity was observed, particularly, when bulky substituents are present in the substrates.

Considering the low reactivity of the transient allylstannanes and the well-known functional group tolerance of

[a] Prof. Dr. K. J. Szabó, M. Sc. O. A. Wallner
Stockholm University, Arrhenius Laboratory
Department of Organic Chemistry
106 91 Stockholm (Sweden)
E-mail: kalman@organ.su.se

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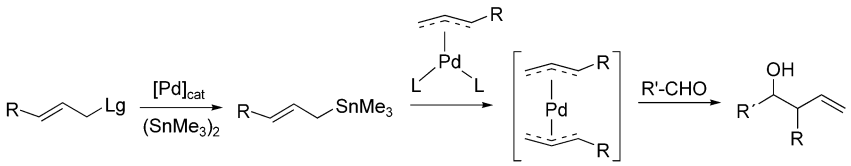
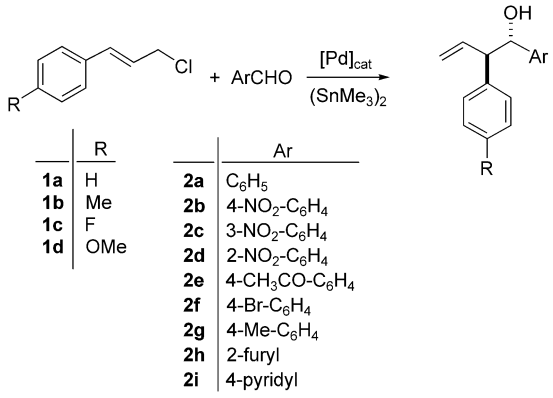


Scheme 2. Palladium-catalyzed formation of transient allylstannane followed by addition to electrophiles via a bis(allyl)palladium intermediate.

palladium catalysis,[24] this transformation offers a flexible synthetic route for allylic substitution by electrophilic reagents. However, the nature of the electronic and steric effects determining the regio- and stereoselectivity in this novel transformation have remained unexplored. In this study we present our results on the possibilities to further extend the synthetic scope of the palladium-catalyzed regio- and stereoselective electrophilic substitution of allyl chlorides. In particular, we have investigated the influence of various aryl substituents on the stereochemical outcome of the reaction. Furthermore, we performed DFT calculations to understand the nature of the steric and electronic interactions governing the selectivity of the catalytic reactions.

Results and Discussion

Experimental studies: Employment of 5 mol% [{(η^3-allyl)-PdCl}$_2$] catalyst (Scheme 3) facilitated the reaction of various allyl chlorides (**1a–d**) with different aldehydes (**2a–i**) in the presence of a stoichiometric amount of hexamethylditin (Table 1). The catalytic reactions proceed under mild



Scheme 3. Experimentally studied palladium-catalyzed electrophilic substitution reactions.

neutral conditions giving the corresponding homoallyl alcohol products (**3a–l**) in good to excellent yield. It was found that in many cases the addition rate of hexamethylditin has a great influence on the yield of the reaction. A rapid addition often leads to precipitation of amorphous palladium black, which deactivates the catalyst before a full conversion of the substrates. Slow addition helps to keep the catalyst in solution, thus improving the yield of the reaction.

The regioselectivity of the reaction is excellent, as the substitution takes place exclusively at the more substituted allylic terminus. As we reported before,[10, 11] this selectivity feature is typical for the palladium-catalyzed electrophilic substitution reactions. The synthetic scope of the reaction is broad due to a high level of functional group tolerance. The nitro-benzaldehyde derivatives (**2b–d**) resist both the Cannizzaro reaction and reduction of the nitro functionality, which may take place under basic conditions and on using low-valent metals (e.g. $SnCl_2$, Scheme 1).[25]

The carbonyl functionality of **2e** also remains intact under the applied reaction conditions (Table 1, entry 7). This indicates that the reaction is highly chemoselective, since the aldehyde functionality can be manipulated in the presence of a keto group. The aromatic bromo functionality (**2f**, Table 1, entry 8) is also tolerated. Oxidative addition of palladium to the C–Br bond was not observed. Heteroaromatic aldehydes, such as furyl (**2h**) and pyridyl (**2i**) derivatives, can also be employed under the standard reaction conditions.

The diastereomeric ratio of the reaction varies from 5:1 (Table 1, entries 4 and 11) to 19:1 (Table 1, entry 9), and the major diastereomer is always the *anti* form. Activated aldehydes usually react with lower stereoselectivity (Table 1, entries 2–8) than benzaldehyde itself (Table 1, entries 1 and 9). The sterically bulky *ortho*-nitro derivative (**2d**) reacts with higher selectivity than the *para*- (**2b**) and *meta*-nitro (**2c**) analogues (c.f. Table 1, entries 4–6). The diastereoselectivity

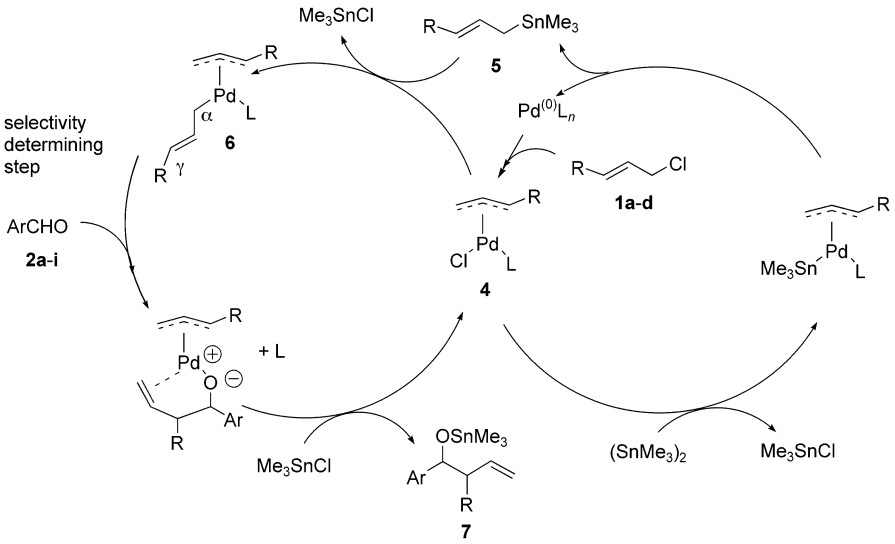
Table 1. Palladium-catalyzed allylic substitution of **1a–d** in the presence of hexamethylditin.

Entry[a]	Substrates		Product			Yield[c]	d.r.[d]
			R[b]	Ar			
1	**1a**	**2a**	H	C_6H_5	**3a**	80	14:1
2	**1b**	**2b**	Me	4-$NO_2C_6H_4$	**3b**	85	7:1
3	**1c**	**2b**	F	4-$NO_2C_6H_4$	**3c**	78	10:1
4	**1d**	**2b**	OMe	4-$NO_2C_6H_4$	**3d**	90	5:1
5	**1d**	**2c**	OMe	3-$NO_2C_6H_4$	**3e**	94	7:1
6	**1d**	**2d**	OMe	2-$NO_2C_6H_4$	**3f**	91	11:1
7	**1d**	**2e**	OMe	4-$CH_3COC_6H_4$	**3g**	93	10:1
8	**1d**	**2f**	OMe	4-BrC_6H_4	**3h**	80	14:1
9	**1d**	**2a**	OMe	C_6H_5	**3i**	60	19:1
10	**1d**	**2g**	OMe	4-MeC_6H_4	**3j**	57	18:1
11	**1d**	**2h**	OMe	2-furyl	**3k**	67	5:1
12	**1d**	**2i**	OMe	4-pyridyl	**3l**	71	7:1

[a] All reactions were conducted using 5 mol% [{(η^3-allyl)PdCl}$_2$] catalyst with slow addition of $(SnMe_3)_2$ in THF at 40 °C. [b] See Scheme 3 for abbreviation. [c] Yield of isolated product. [d] Diastereomer ratio (*anti*/*syn*).[9]

also depends on the substituent effects in the allylic substrates. The methoxy derivative (**1d**) generates a more reactive nucleophile than the fluoro derivative (**1c**). Comparison of entries 3 and 4 in Table 1 reveals that the more reactive allylic substrate reacts with a lower selectivity. Thus the stereoselectivity of the reaction appears to be inversely proportional to the reactivity of the allylic substrate and the electrophile.

Mechanistic aspects: The catalytic electrophilic substitution reaction proceeds via two coupled catalytic cycles (Scheme 4). The two cycles are linked by (η^3-allyl)palladium complex **4**, which is generated by oxidative addition of **1** to palladium(0). The reaction of hexamethylditin results in the transient allylstannane (**5**).[26] It is well documented[12, 13] that allylstannanes readily undergo transmetalation with (η^3-allyl)palladium complexes to give bis(allyl)palladium complexes. Accordingly, bis(allyl)palladium complex **6** can be formed from **4** and



Scheme 4. Catalytic cycle of the palladium-catalyzed electrophilic substitution process.

5 under the catalytic conditions. Subsequently, complex **6** reacts with electrophiles to provide the final product **7**.

The electrophilic attack on the bis(allyl)palladium intermediate **6** by the electrophiles **2** is probably the most important step of the catalytic reaction, since this step determines the regio- and stereochemical outcome of the catalytic transformation. Understanding the nature of the steric and electronic effects governing this process is particularly important, since the mechanistic aspects of the development of regio- and stereoselectivity in palladium-catalyzed electrophilic substitution has not been studied before. Therefore, we have performed theoretical studies on the selectivity determining step of the above described reaction. As a model reaction, we have chosen the electrophilic substitution of cinnamyl chloride (**1a**) with benzaldehyde (**2a**), which gives homoallyl alcohol **3a** with high regio- and stereoselectivity (Table 1, entry 1).

Computational methods: All geometries were fully optimized by employing a Becke-type[27] three-parameter density functional model B3PW91 (Figure 1). This so-called hybrid functional includes the exact (Hartree–Fock) exchange, the gradient corrected exchange functional of Becke,[27] and the more recent correlation functional of Perdew and Wang.[28] All calculations have been carried out using a double-ζ(DZ) + P basis constructed from the LANL2DZ basis[29–31] by adding one set of d-polarization functions to the heavy atoms (exponents: C 0.63, O 1.154) and one set of diffuse d-functions on palladium (exponent: 0.0628). Harmonic frequencies have been calculated at the level of optimization for all structures to characterize the calculated stationary points and to determine the zero-point energies (ZPE). Fully optimized transition-state structures **9b**, **9d**, **10b**, **10d**, **11b**, and **12b** have been characterized by a single imaginary frequency, while the rest of the optimized structures possess only real frequencies. All calculations have been carried out by employing the Gaussian 98 program package.[32]

Structure and stability of the η^3,η^3-coordinated complexes: Four different η^3,η^3-coordinated bis(allyl)palladium complexes are expected to form, when one phenyl substituent is attached to each allyl moiety. In complexes **8a**, **b** (Figure 1) the allyl moieties are in a *trans* orientation, while in **8c, d** the allyl groups are *cis*-oriented. Similarly to the unsubstituted analogue,[16] the energy difference between the different forms is small, however the *trans* complex is somewhat more stable than the *cis* form. Interestingly, in the most stable isomer (**8a**) the phenyl substituents are located on the adjacent allylic termini.

Structure and stability of the η^1,η^3-coordinated complexes: It is well established that η^1,η^3-bis(allyl)palladium complexes easily form from the η^3,η^3-analogues by coordination of an external ligand.[16, 33] The catalytic reactions were conducted in the absence of strongly coordinating ligands (such as phosphines), under so-called "ligand-free" conditions. However, the DFT calculations indicate that the electrophilic substrate (**2a**) has a fairly good coordination ability to palladium (**9a**, **10a**, **11a**, and **12a**). Formation of the η^1,η^3-complexes by coordination of benzaldehyde to **8a** is an endothermic process. The stability of these species is highly dependent on the location of the phenyl group on the allyl moieties. In the most stable form (**9a**) the phenyl substituent is attached to the γ-carbon atom of the η^1-moiety and the η^3-phenyl group is attached to the allylic terminus *trans* to the η^1-allyl group. The corresponding complex, in which the phenyl group is attached to the α-carbon atom of the η^1-allyl (**11a**) is considerably (by

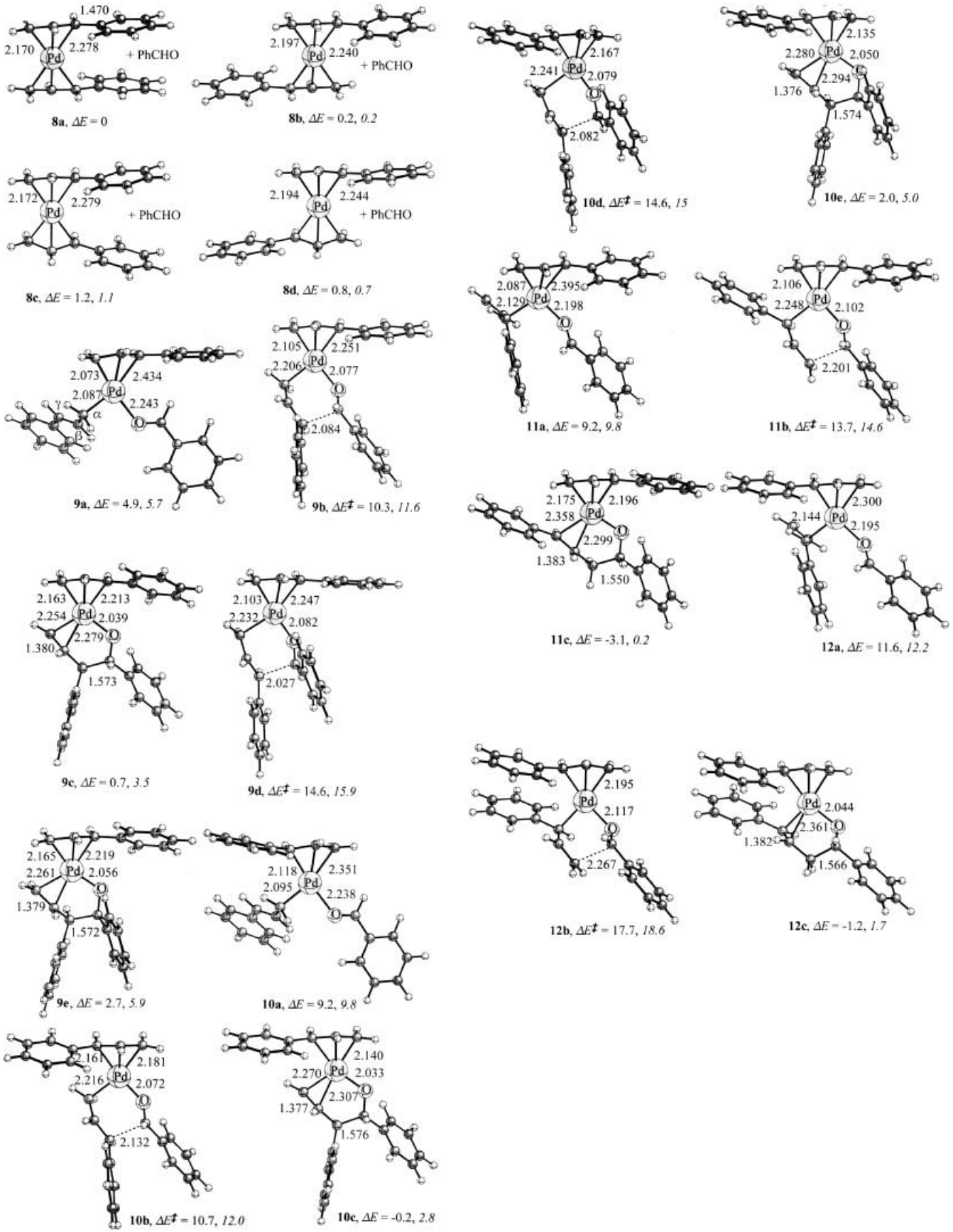


Figure 1. Calculated structure and stability of the bis(allyl)palladium species. The energy values are given in kcal mol^{-1} and the bond lengths are given in Å. The ZPV corrected energies are given in italics.

4.1 kcal mol^{-1}) less stable. Clearly, substitution of the metalated carbon atom (C_α) strongly destabilizes the η^1,η^3 complexes.[10, 11, 16–18] When both phenyl groups are on the same side of the complex (**10a** and **12a**), the steric interactions lead to a low stability.

Regioselectivity of the electrophilic attack: The electrophilic substitution reactions takes place through six-membered cyclic transition states, in which the distance between the forming carbon–cabon bond varies between 2.08 and 2.26 Å. The lowest energy path (11.6 kcal mol^{-1}) involves **9b** (Figure 2), which bears the phenyl substituent at the γ-position of the η^1-allyl moiety. This reaction path leads to slightly endothermic (3.5 kcal mol^{-1}) formation of the branched allylic product **9c**. Formation of the unbranched product **11c** proceeds through a much higher activation barrier (15.9 kcal mol^{-1}). When the phenyl substituent of the η^3-ligand and the phenyl substituent of the η^1-moiety are located on the same side of the complex, the reaction profiles (**10a** → **10b** → **10c** and **12a** → **12b** → **12c**) are similar to the above, however the activation energies are much higher.

Stereoselectivity of the electrophilic attack: Formation of the branched allylic product may proceed by formation of four different complexes. The above discussed processes lead to **9c** and **10c**, in which the phenyl groups are in *anti* configuration. However, by changing the relative orientation of the η^1-moiety and the benzaldehyde molecule, two other products can be obtained (**9e** and **10e**) in which the phenyl groups are mutually *syn*. Formation of *syn* complexes **9e** and **10e** proceeds through TS structures **9d** and **10d**, respectively. The activation barrier (Figure 2) to the formation of these *syn* products is considerably higher (by 4.0–4.3 kcal mol^{-1}) than the activation barrier (**9b** and **10b**) for formation of *anti* products (**9c** and **10c**). This result is in good agreement with the experimental results (Table 1) that the major product of the palladium-catalyzed electrophilic substitution is the branched allylic product with *anti* stereochemistry.

Inspection of the reoriented TS geometries (Figure 3) reveals the underlying substituent effects governing the stereochemistry of the reaction. The six-membered TS has a pronounced chair conformation as indicated by the red bars. In **9b** leading to the *anti* product **9c** the phenyl groups are in *trans*-diequatorial positions across the newly forming carbon–carbon bond, while in TS structure **9d** (which provides the *syn* product **9e**) the phenyl group of benzaldehyde is axial and the η^1-allylic phenyl group is equatorial. Accordingly, in **9d** the axial phenyl group is involved in a destabilizing steric interaction with the η^3-allyl moiety of the complex, which explains its low stability. Interestingly, the activation barrier for the reverse process (**9c** → **9b** → **9a**) is lower for the *anti* product **9c** (8.1 kcal mol^{-1}) than that for the corresponding (**9e** → **9d** → **9a**) process for the *syn* product **9e** (10.0 kcal mol^{-1}). This suggests that the decomposition of the *syn* product (**9e**) is somewhat more difficult than the decomposition of the *anti* product (**9c**), which explains the fact that a small amount of *syn* isomer (*anti*/*syn* ratio is 14:1, Table 1) is also formed under catalytic conditions.

There are many highly stereoselective transformations proceeding through six-membered cyclic transition states. However, an important new feature in the process described above is that the sterically demanding substituted η^3-allyl moiety controls the stereoselection of the reaction. Employment of this new way of stereoinduction can be useful in development of novel highly stereoselective catalytic transformations.

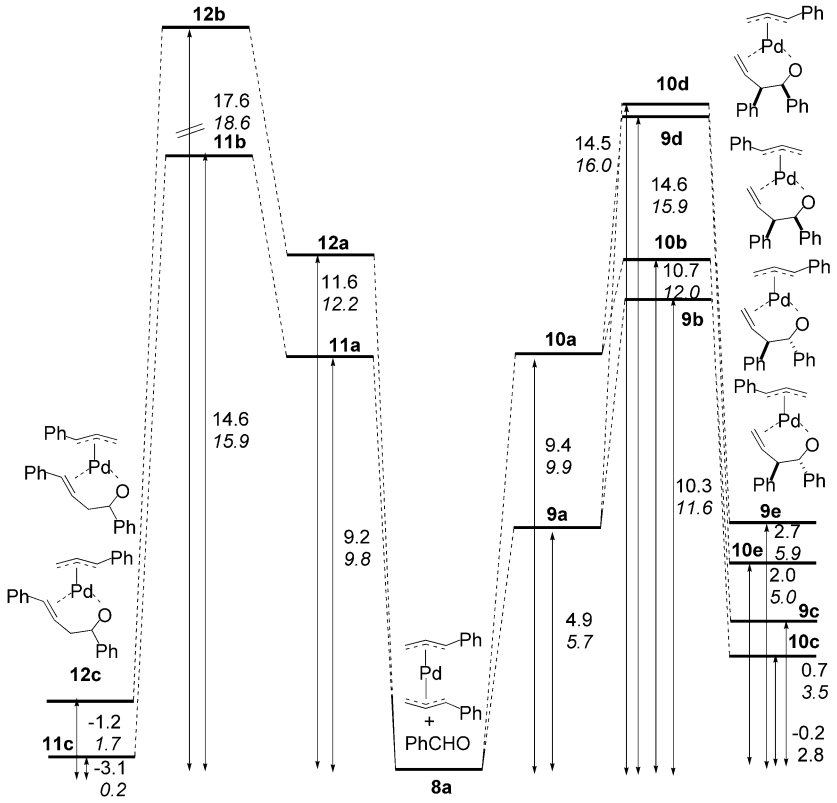


Figure 2. Reaction profiles for the electrophilic attack resulting different regio- and stereoisomers. The energies are given in kcal mol^{-1}.

Conclusions

In this study we have shown that palladium catalysis can be applied for electrophilic allylic substitution of aromatic allyl chlorides in the presence of hexamethylditin. This reaction proceeds with high regio- and stereoselectivity for various aldehyde electrophiles. Many functionalities involving aromatic NO_2, CH_3CO, Br, and F substituents are tolerated; and the reaction

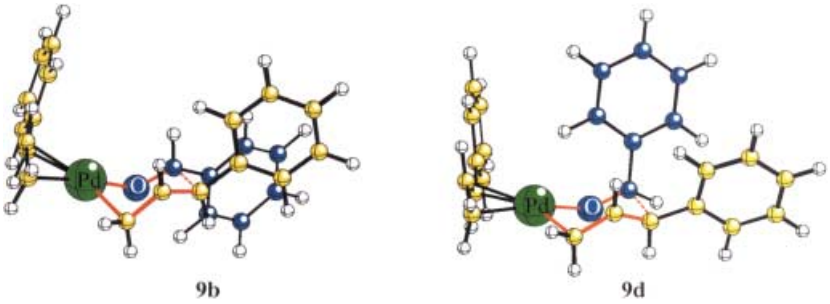


Figure 3. Side-view presentation of **9b** and **9d** to illustrate the chair conformation of the cyclic six-membered TS structures.

can also be extended to heteroaromatic substrates. Density functional calculations were undertaken to study the development of the selectivity in the reaction. The theoretical results show that the two most important factors controlling the selectivity are: the location of the phenyl functionality in the η^1-moiety of the bis(allyl)palladium intermediate; and the relative configuration of the phenyl substituents in the cyclic six-membered transition state of the reaction. The lowest energy path corresponds to the **8a** → **9a** → **9b** → **9c** process providing the branched allylic isomer, in which the phenyl groups are in *anti* configuration. These computational results are in excellent agreement with the experimental catalytic results presenting the same regio- and stereoselectivity for the product.

The stereo- and regioselectivity of the above palladium-catalyzed electrophilic substitution reactions are controlled by new mechanistic features. Employment of these novel elements in the development of catalytic transformations offers a new alternative route for the regio- and stereoselective synthesis of densely functionalized allylic synthons.

Experimental Section

General procedure for allylation of aldehydes 2a–2i with cinnamyl chlorides 1a–d: The corresponding aldehyde (**2a–2i**) (0.30 mmol), cinnamyl chloride **1a–d** (0.36 mmol), and η^3-allylpalladium chloro dimer (2.7 mg, 0.0075 mmol) were dissolved in THF (2.3 mL) containing 4 Å molecular sieves (70 mg) and heated to 40 °C. Hexamethylditin (118 mg, 0.36 mmol) in THF (0.7 mL) was added over a period of 12 h to this reaction mixture by using a syringe pump, and then the reaction mixture was stirred for additional 12 h at 40 °C. After evaporation of the solvent the crude product was purified by silica gel chromatography. Further experimental details and characterization of **3b–l** are given in the Supporting Information.

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[1] J. A. Marshall, *Chem. Rev.* **2000**, *100*, 3163.
[2] S. Araki, T. Kamei, T. Hirashita, H. Yamamura, M. Kawai, *Org. Lett.* **2000**, *2*, 847.
[3] Y. Tamaru, *J. Organomet. Chem.* **1999**, *576*, 215.
[4] M. Kimura, I. Kiyama, T. Tomizawa, Y. Horino, S. Tanaka, Y. Tamaru, *Tetrahedron Lett.* **1999**, *40*, 6795.
[5] Y. Masuyama, N. Kinugawa, Y. Kurusu, *J. Org. Chem.* **1987**, *52*, 3702.
[6] Y. Masuyama, K. Otake, Y. Kurusu, *Tetrahedron Lett.* **1988**, *29*, 3563.
[7] K. Yasui, Y. Goto, T. Yajima, Y. Taniseki, K. Fugami, A. Tanaka, *Tetrahedron Lett.* **1993**, *34*, 7619.
[8] Y. Tamaru, A. Tanaka, K. Yasui, S. Goto, S. Tanaka, *Angew. Chem.* **1995**, *107*, 862; *Angew. Chem. Int. Ed.* **1995**, *34*, 787.
[9] J. P. Takahara, Y. Masuyama, Y. Kurusu, *J. Am. Chem. Soc.* **1992**, *114*, 2577.
[10] O. A. Wallner, K. J. Szabó, *Org. Lett.* **2002**, *4*, 1563.
[11] O. A. Wallner, K. J. Szabó, *J. Org. Chem.* **2003**, *68*, 2934.
[12] A. Goliaszewski, J. Schwartz, *Tetrahedron* **1985**, *41*, 5779.
[13] H. Nakamura, H. Iwama, Y. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 6641.
[14] H. Nakamura, J.-G. Shim, Y. Yamamoto, *J. Am. Chem. Soc.* **1997**, *119*, 8113.
[15] H. Nakamura, K. Aoyagi, J.-G. Shim, Y. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 372.
[16] K. J. Szabó, *Chem. Eur. J.* **2000**, *6*, 4413.
[17] N. Solin, S. Narayan, K. J. Szabó, *J. Org. Chem.* **2001**, *66*, 1686.
[18] N. Solin, S. Narayan, K. J. Szabó, *Org. Lett.* **2001**, *3*, 909.
[19] S. A. Godleski, in *Nucleophiles with Allyl-Metal Complexes, Vol. 4* (Eds.: B. M. Trost, I. Fleming), Pergamon New York, **1991**, p. Chapter 3.3.
[20] B. M. Trost, *Acc. Chem. Res.* **1980**, *13*, 385.
[21] B. M. Trost, *Acc. Chem. Res.* **1996**, *29*, 355.
[22] B. Åkermark, K. Zetterberg, S. Hansson, B. Krakenberger, A. Vitagliano, *J. Organomet. Chem.* **1987**, *335*, 133.
[23] K. J. Szabó, *Chem. Soc. Rev.* **2001**, *30*, 136.
[24] J. Tsuji, *Palladium Reagents and Catalysis: Innovations in Organic Synthesis*, Wiley, Chichester, **1995**.
[25] M. Parra, R. Mestres, D. Aparicio, N. Durana, G. Rubiales, *J. Chem. Soc. Perkin I* **1989**, 327.
[26] N. A. Bumagin, A. N. Kasatkin, I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim. (Engl. Transl.)* **1984**, 636.
[27] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.
[28] J. P. Perdew, Y. Wang, *Phys. Rev. B* **1992**, *45*, 13244.
[29] T. H. Dunning, P. J. Hay, *Modern Theoretical Chemistry, Vol. 3*, Plenum, New York, **1977**.
[30] P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 270.
[31] P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299.
[32] Gaussian 98 (Revision A.7), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**.
[33] J. Krause, R. Goddard, R. Mynott, K.-R. Pörschke, *Organometallics* **2001**, *20*, 1992.

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