Unusual Selectivity-Determining Factors in the Phosphine-Free Heck Arylation of Allyl Ethers

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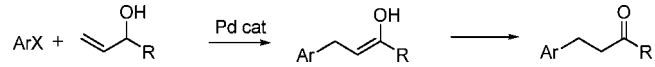
The Heck reaction of aryl iodides and bromides with allyl ethers has been investigated. Using phosphine-free $Pd(OAc)_2$ in DMF at 90 °C in the presence of Bu_4NOAc, the reaction gave cinnamyl derivatives, usually in good to high yields, with a wide range of aryl halides. The reaction tolerates a variety of functional groups, including ether, amide, alcohol, aldehyde, ketone, ester, cyano, carboxylic acid, and nitro groups. Ortho-substituted arylating agents afforded moderate yields in some cases, though good to high yields were obtained with *o*-iodotoluene, iodovanillin, and 1-iodonaphthalene. Several pieces of experimental evidence suggest that the observed selectivity in formation of the vinylic substitution products is kinetic in origin under these conditions. A DFT investigation has been performed to clarify the source of product selectivity and, in particular, the preference for cinnamyl ether over enol ether products. Interestingly, it was found that the product selectivity does not arise from competing β-hydride eliminations but rather from a competition between β-elimination and hindered single-bond rotation in the initial carbopalladation product.

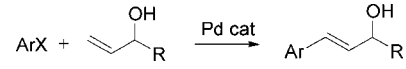
Introduction

The palladium-catalyzed reaction of aryl halides with allylic alcohols has proved to be a useful method for the preparation of β-aryl aldehydes and ketones, which have been obtained as the main or sole products under a variety of reaction conditions[1–6] (Scheme 1).

Scheme 1. Arylation of Allylic Alcohols Giving Carbonyl Compounds



Scheme 2. Arylation of Allylic Alcohols Giving Cinnamyl Derivatives



Attempts to control the reaction outcome to favor the formation of cinnamyl alcohols (Scheme 2) have also been reported. Jeffery[7] prepared cinnamyl alcohols in synthetically useful yields under mild conditions, utilizing stoichiometric amounts of silver acetate or carbonate to alter the course of the reaction. Kang et al.[8a] reported that complete regioselectivity could be obtained using diphenyliodonium tetrafluoroborate as the arylating agent at room temperature. In both cases, the

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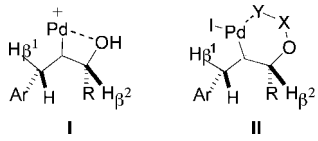
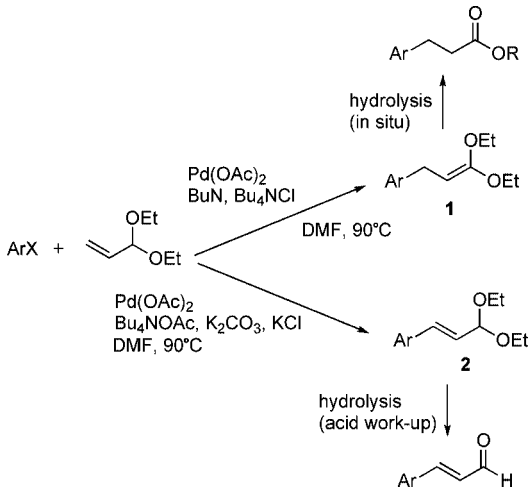


Figure 1. Proposed coordination directing the β-elimination.

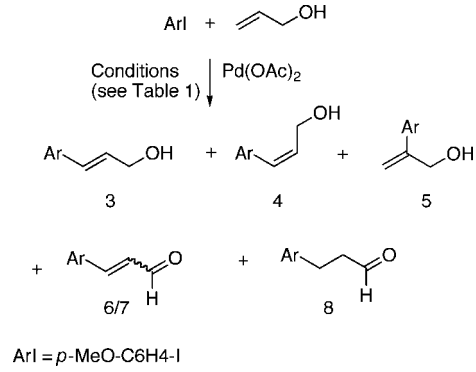
Scheme 3. Selective Formation of 3-Arylpropanoates or Cinnamaldehydes from Acrolein Acetal



involvement of an electron-deficient Pd(II) center has been suggested to play a key role in promoting the formation of the carbopalladation intermediate **I** (where only $H_\beta{}^1$ is located favorably for the syn-β elimination of HPdX). Tamaru and coworkers[9] employed *N*-alkyl-*O*-allyl carbamates in the presence of $Pd(OAc)_2$ and Bu_3P to direct the reaction with aryl iodides toward the formation of cinnamyl derivatives. The role of the auxiliary group is to coordinate the palladium atom to form the six-membered ring intermediate **II** (Figure 1), which disfavors the syn-β elimination of $H_\beta{}^2$Pd. More recently, Doucet, Santelli, et al.[10] studied the reactivity of a variety of protected allylic alcohols with aryl bromides in the presence of the $[PdCl(C_3H_5)]_2$/Tedicyp (*cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphanylmethyl)cyclopentane) precatalyst system and K_2CO_3 in DMF at 130 °C and showed that, in most cases, (*E*)-cinnamyl alcohol derivatives were the major products.

As part of our continuing studies on the Heck reaction, we have recently shown that the proper choice of palladium catalysts, bases, and added salts allows for the selective preparation of cinnamaldehydes[11] or 3-arylpropanoate esters[12] (Scheme 3) from aryl halides and acrolein diethyl acetal[13] (a reaction known to be flawed by the formation of mixtures of vinylic substitution products due to the involvement of both the available β-hydrogens in the key elimination of HPdX species from carbopalladation intermediates). In particular, we have found that the presence of acetate anions, associated with tetrabutylammonium cations, can direct the reaction so as to favor the almost exclusive formation of **2**, which is subsequently converted into the corresponding aldehyde upon hydrolysis.

Scheme 4. Heck Arylation of Allyl Alcohol



On the basis of these results, we became interested in investigating whether the strong directing effect of acetate anions observed in the synthesis of cinnamaldehydes could be exploited in the related arylation of allylic alcohols to provide a simple approach to cinnamyl alcohols from aryl halides.

Herein we report the results of this study and an extension to the use of allyl ethers as substrates. In addition, we have investigated the mechanism by DFT methods.

Results and Discussion

Heck Arylation of Allyl Alcohol. Initial attempts were made using *p*-iodoanisole, a typical electron-rich aryl halide, and allyl alcohol (Scheme 4). Under the same conditions that gave the best results with acrolein diethyl acetal ($Pd(OAc)_2$, K_2CO_3, LiCl, DMF, 90 °C), a mixture of six products was obtained (Table 1, entry 2): the two linear stereoisomeric allyl alcohol derivatives **3** and **4**, the two stereoisomeric β-arylpropenals **6** and **7**, β-arylpropanal **8** (all generated via a carbopalladation leading to the formation of the new carbon−carbon bond at the terminal carbon atom), and the branched allylic alcohol **5**, derived from reverse carbopalladation of allyl alcohol.

Though the result obtained is of limited synthetic value, the reaction nevertheless shows a satisfactory cinnamyl alcohol/β-arylpropanal selectivity. Indeed, compounds **3**, **4**, **6**, and **7** (**6** and **7** are most probably produced via oxidation of the initially formed **3** and **4**) and β-arylpropanal **8** were isolated in approximately 6.44 ratio (Table 1), suggesting that the presence of acetate anions can effectively direct the reaction toward the preferential formation of cinnamyl derivatives. In contrast, a large predominance of aldehyde derivatives (compound **10** is most likely the result of an aldol reaction of **8**) was observed when the reaction was carried out under the same conditions with the omission of Bu_4NOAc (Scheme 5 and Table 1, entry 1).

We have made only a partial investigation of the details of the oxidation reaction yielding **6** and **7**.[14] Of the more common types of oxidation, the involvement by atmospheric oxygen[15] has been ruled out by careful deoxygenation of the reaction mixture. Another reasonable path is ligand exchange in the intermediate (σ-aryl)palladium complexes[16] generating (allyloxy)palladium(II) aryl species, followed by β-elimination, but the subsequent fate of the arylpalladium(II) hydride in this case

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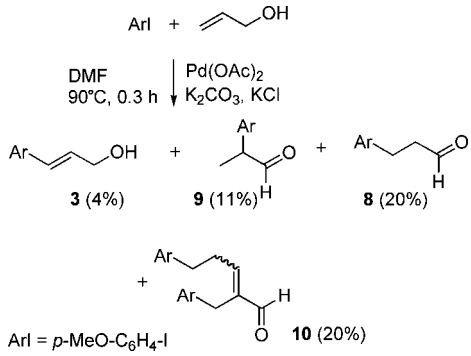
Table 1. Solvents, Bases, Additives, and Temperature in the Palladium-Catalyzed Reaction of *p*-Iodoanisole with Allyl Alcohol[ab]

						yield (%)						
entry	solvent	base (amt (equiv))	additive (amt (equiv))	*T* (°C)	time (h)	total	**3**	**4**	**5**	**6** + **7**	**8**	(**3** + **4** + **6** + **7**)/**8**
1[c]	DMF	K_2CO_3 (1.5)	KCl (1)	90	0.3	75[d]	4				60[e]	0.07[f]
2[g]	DMF	K_2CO_3 (1.5), Bu_4NOAc (2)	KCl (1)	90	2	83	37	3	16	18	9	6.4
3	DMA	K_2CO_3 (1.5), Bu_4NOAc (2)	KCl (1)	90	3	88	40	1	15	32	1	73
4	DMF	Bu_4NOAc (2)		90	0.3	99	48	3	20	10	18	3.4
5	DMF	Bu_4NOAc (2)		60	2	84	50		21	6	7	8
6	toluene	Bu_4NOAc (2)		90	1	49			22	15	12	1.2

[a] Unless otherwise indicated, reactions were carried out under an argon atmosphere on a 1.28 mmol scale using 1 equiv of *p*-iodoanisole, 1.5 equiv of allyl alcohol, and 0.03 equiv of $Pd(OAc)_2$ in 3 mL of solvent. [b] Unless otherwise indicated, yields are based on NMR analysis of samples containing mixtures of compounds **3**−**8** obtained by chromatography. [c] Yields are given for isolated products. [d] Including **9** (Scheme 5). [e] Including **10** (Scheme 5). [f] Calculated as the ratio between **3** and **8** + **10**. [g] 3 equiv of allyl alcohol.

Scheme 5. Heck Arylation without Added Acetate, Giving >60% Aldehyde Initially (Each 10 Equals Two 8)

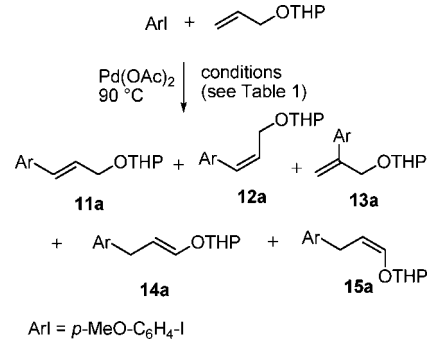


should be reductive elimination to generate anisole, which could be detected in only trace amounts. It seems therefore that oxidation products might involve the intermediacy of palladaoxetanes[17] or the oxidative addition of Pd(0) species to the oxygen−hydrogen bond of the allylic alcohols followed by the elimination of HPdH from the resultant alkoxypalladium hydride intermediates.[18]

The reaction conditions were then modified in attempts to increase the yields of, and selectivity for, the cinnamyl product and possibly to limit the oxidation processes. However, no significant improvements were obtained. The formation of the β-arylpropanal **8** was almost completely suppressed in DMA, but stereoisomeric oxidation compounds **6** and **7** were obtained in higher yield (Table 1, entry 3). Lowering the reaction temperature to 60 °C in DMF and omitting K_2CO_3 and KCl (Table 1, entry 5) led to a decrease of oxidation products and a very high ratio of **3** to **4**. However, compound **3** was isolated in only moderate yield (albeit slightly higher than under the conditions shown in Table 1, entry 2) along with significant amounts of the regioisomer **5**. When the reaction was carried out in toluene, compound **5** was isolated as the main product and there was no evidence for formation of the isomeric cinnamyl alcohols **3** and **4** (Table 1, entry 6). In view of these results, and in order to bypass the oxidation problems, we decided to explore the utilization of the THP derivative of allyl alcohol as substrate.

Heck Arylation of 2-(Allyloxy)tetrahydropyran. The reaction of 2-(allyloxy)tetrahydropyran[19] with *p*-iodoanisole was found to give five products (Scheme 6): **11a**, **12a**, **14a**, and **15a** (all generated via a 3-arylation reaction) and the branched derivative **13a**. Some results of our optimization work, using

Scheme 6. Heck Arylation of THP Allyl Ether



$Pd(OAc)_2$ as the source of Pd(0) species at 90 °C and a variety of solvents, bases, and additives, are summarized in Table 2.

Good results were obtained under a variety of conditions using Bu_4NOAc in combination with carbonate bases and/or halide anions (Table 2, entries 1−4) but the best results in terms of reaction time, yield of **11a**, linear/branched arylation ratio, cinnamyl/enol ether ratio ((**11a** + **12a**)/(**14a** + **15a**)), and simplicity of conditions were obtained when the reaction was carried out in the presence of Bu_4NOAc, omitting carbonate bases and other additives (Table 2, entry 5). With Et_3N, with or without Bu_4NCl (Table 2, entries 8 and 9), or under typical Jeffery conditions[20] (Table 2, entry 10) the reaction afforded lower yields of **11a** and lower (**11a** + **12a**)/(**14a** + **15a**) ratios. The implication of these data is that acetate anions can effectively influence the reaction course so as to favor the formation of cinnamyl derivatives. Of note is that their efficacy depends on the associated cationic species, acetate anions associated with larger cations being found to give the best results, with the (**11a** + **12a**)/(**14a** + **15a**) ratio decreasing in the order $Bu_4N^+ > Cs^+ > K^+$ (Table 2, entries 5−7). The involvement of solubility and ion-pairing effects, controlling the concentration of the available acetate anions, are most probably the main factors accounting for the observed results.

When the "optimal" procedure ($Pd(OAc)_2$, Bu_4NOAc, DMF, 90 °C) was extended to ethyl *p*-iodobenzoate, a typical electron-poor aryl halide, a decrease in efficiency was observed and the corresponding cinnamyl alcohol was obtained in only 58% yield together with a mixture of regio- and stereoisomeric derivatives. Increasing the excess of the tetrahydropyranyl derivative of the allyl alcohol to 3 equiv led to the formation of the desired product in 78% yield (Table 3, entry 25).

Therefore, two general reaction conditions were employed when the arylation was extended to include other aryl iodides and bromides, both using $Pd(OAc)_2$ and Bu_4NOAc in DMF at 90 °C and differing in the excess of 2-(allyloxy)tetrahydropyran.

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Table 2. Bases and Additives in the Palladium-Catalyzed Reaction of *p*-Iodoanisole with 2-(Allyloxy)tetrahydropyran[a,b]

				yield (%)						
entry	base (amt (equiv))	additive (amt (equiv))	time (h)	total	**11a**	**12a**	**13a**	**14a**	**15a**	(**11a** + **12a**)/(**14a** + **15a**)
1	K_2CO_3 (1.5), Bu_4NOAc (2.0)	KCl (1.0)	1	99	74	5	10	6	4	7.9
2	Cs_2CO_3 (1.5), Bu_4NOAc (2.0)		8	90	68	4	8	5	5	7.2
3	K_2CO_3 (1.5), Bu_4NOAc (2.0)		1	100	73	4	10	5	8	5.9
4	Na_2CO_3 (1.5), Bu_4NOAc (2.0)		1	98	60	5	11	11	11	3.0
5	Bu_4NOAc (2.0)		0.5	100	73	6	11	6	4	7.9
6	CsOAc (2.0)		6	96	60	4	13	10	9	3.4
7	KOAc (2.0)		12	98	63	2	10	11	12	2.8
8	Et_3N (3.0)		48	58	27	traces	2	12	17	0.9
9	Et_3N (2.0)	Bu_4NCl (1.0)	1	78	50	1	2	8	17	2.0
10	K_2CO_3 (1.5)	Bu_4NCl (1.5)	2	82	55	traces	traces	10	17	2.0
11	Bu_4NOAc (2.0)	Bu_4NBr (1.5)	2	80[c]	57	5	9	7	2	6.9

[a] Reactions were performed on a 1.28 mmol scale under an argon atmosphere using 1 equiv of *p*-iodoanisole, 1.5 equiv of 2-(allyloxy)tetrahydropyran, and 0.03 equiv of $Pd(OAc)_2$ in 3 mL of DMF. [b] Yields are based on NMR analysis of samples containing mixtures of compounds **11a**−**15a** obtained by chromatography. [c] In the absence of DMF.

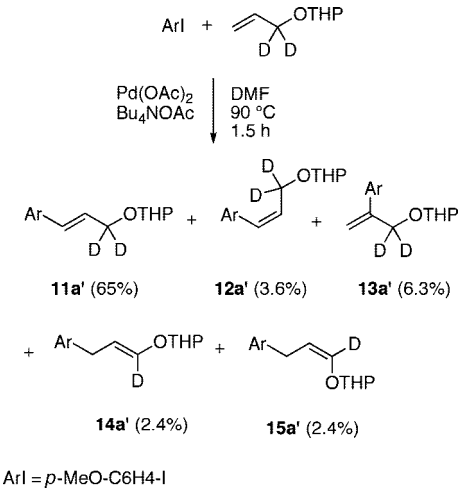
Table 3. Heck Arylation of 2-(Allyloxy)tetrahydropyran with Aryl Halides in the Presence of Tetrabutylammonium Acetate[a,b]

Entry	Aryl halide		Time (h)	yield of **11** (%)
1[c]	*p*-MeO-C_6H_4-I	**a**	0.5	73
2[c]	*p*-MeO-C_6H_4-Br	**a**	12	62
3[c]	*m*-MeO-C_6H_4-I	**b**	0.2	71
4[c]	*m*-MeO-C_6H_4-Br	**b**	12	71
5[c]	*o*-MeO-C_6H_4-I	**c**	24	37
6[c]	3,5-Me_2-C_6H_3-Br	**d**	24	55
7[c]	*p*-Me-C_6H_4-I	**e**	1.5	70
8[c]	*m*-Me-C_6H_4-I	**f**	1.5	70
9[c]	*o*-Me-C_6H_4-I	**g**	1.5	69
10[c]	*m*-$HOCH_2$-C_6H_4-I	**h**	1	55
11	2-OH-3-MeO-5-CHO-C_6H_2-I	**i**	4	87
12[c]	PhI	**j**	1	70
13[c]		**k**	1	61
14	*m*-F-C_6H_4-I	**l**	1	70
15	*p*-F-C_6H_4-I	**m**	1	75
16	*p*-F-C_6H_4-Br	**m**	8	57
17	*p*-Cl-C_6H_4-Br	**n**	1	58
18	*m*-CF_3-C_6H_4-I	**o**	1	67
19	*m*-CF_3-C_6H_4-Br	**o**	1.5	76
20	*p*-CN-C_6H_4-Br	**p**	1	55
21	*p*-COOH-C_6H_4-Br	**q**	4	57
22	*m*-COOEt-C_6H_4-I	**r**	0.5	69
23	*m*-NO_2-C_6H_4-I	**s**	1	57
24[c]	*o*-Br-C_6H_4-I	**t**	12	48
25	*p*-COOEt-C_6H_4-I	**u**	4	78[d]
26	*p*-MeCO-C_6H_4-Br	**v**	1	62

[a] Unless otherwise stated, reactions were performed on a 1.28 mmol scale under an argon atmosphere using 1 equiv of aryl halide, 3 equiv of 2-(allyloxy)tetrahydropyran, 0.03 equiv of $Pd(OAc)_2$, and 2 equiv of Bu_4NOAc in 3 mL of DMF. [b] Yields are given for isolated products. [c] 1.5 equiv of 2-(allyloxy)tetrahydropyran. [d] Compound **11u** was isolated in 58% yield in the presence of 1.5 equiv of 2-(allyloxy)tetrahydropyran.

Under these conditions the reaction usually gives vinylic substitution products **11** in good to high yields with many neutral, electron-rich, and electron-poor aryl halides. Ether, amide, alcohol, aldehyde, ketone, ester, cyano, carboxylic acid, and nitro groups are well tolerated. The results obtained during this study are summarized in Table 3. As expected, reactions with electron-rich aryl bromides are usually slower than with the corresponding aryl iodides. With ortho-substituted arylating agents the reaction afforded moderate yields in some cases (Table 3, entries 5 and 24), though good to high yields were obtained with *o*-iodotoluene, iodovanillin, and 1-iodonaphthalene (Table 3, entries 9, 11, and 13).

Scheme 7. No Deuterium Scrambling, Indicating Irreversible β-Hydride Elimination



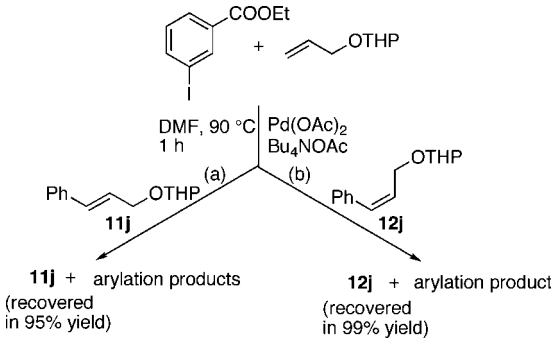
Kinetic vs Thermodynamic Control. The strong tendency of the THP derivative of allyl alcohol to generate cinnamyl derivatives in the presence of Bu_4NOAc might entail either thermodynamic control, with an equilibration step following the initial elimination reaction, or a kinetically controlled process. The latter would include a syn carbopalladation by which the new carbon−carbon bond is formed predominantly at C3 followed by a syn β-elimination of HPdX involving preferentially the benzylic hydrogen.

In order to differentiate between these two working hypotheses, we treated $CH_2{=}CHCD_2OTHP$[21] with *p*-iodoanisole in the presence of $Pd(OAc)_2$ and Bu_4NOAc in DMF at 90 °C for 1.5 h (Scheme 7). No scrambling of deuterium was observed, showing that under these conditions the product distribution is kinetic in origin. A similar result was obtained using Et_3N as the base, the product distribution and overall yield being consistent with those obtained when $CH_2{=}CHCH_2OTHP$ was employed (Table 2, entry 8).

The absence of any positional and stereochemical isomerization process following the β-elimination step is further

(21) The required THP derivative of allyl-1,1-d_2 alcohol was prepared according to the method described by: Schuetz, R. D.; Millard, F. W. *J. Org. Chem.* **1959**, *24*, 297–300.

Scheme 8. No Scrambling of Product Stereochemistry in the Title Reaction



supported by the following experiments. 2-(Allyloxy)tetrahydropyran was subjected to the optimized conditions, producing vinylic substitution products in the presence of ethyl *m*-iodobenzoate and a pure sample of **11j** (Scheme 8a). The product distribution and the overall yield of the arylation reaction were similar to those reported in Table 3, entry 22. Compound **11j** was recovered in almost quantitative isolated yield, and its stereochemistry was maintained. A similar result was obtained with the cis isomer **12j**[22] (Scheme 8b).

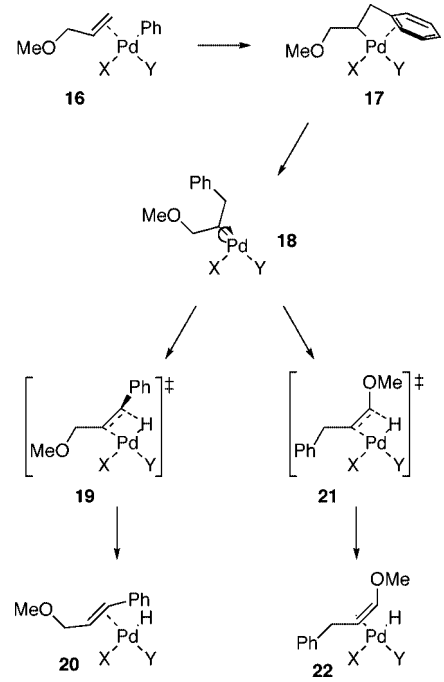
As far as the stereochemistry of **11j** and **12j** is concerned, analogous results were also obtained when pure samples of **11j** and **12j** were treated with ethyl *m*-iodobenzoate and 2-(allyloxy)tetrahydropyran in the presence of Et_3N and Bu_4NCl at 90 °C in DMF for 2 h (both **11j** and **12j** were recovered in 85% yield).

Modeling Studies. In order to understand the mechanism behind the acetate-induced regioselectivity in particular, and to improve our understanding of the β-hydride elimination step of the Heck reaction in general, we decided to investigate the reaction by means of DFT calculations. Mechanistic studies of the β-elimination step of the Heck reaction in the past are scarce, since the β-elimination occurs in the middle of the catalytic cycle, which hampers kinetic experiments.[23]

We have chosen two sets of experiments as basis for the calculations: the simplest conditions that induce both a high regioselectivity and a high rate (Table 22, entry 5) and a set of conditions that result in a low selectivity without a significant drop in reaction rate (Table 2, entry 10). In the former case a ratio of approximately 8:1 between cinnamyl and enol ether is obtained, which corresponds to a free energy difference of 6 kJ/mol at 90 °C. The latter conditions gave a product ratio of 2:1, corresponding to ca. 2 kJ/mol. We assume that at least one anionic ligand coordinates to palladium,[24] since the alternative would be a cationic cycle,[25] where Markovnikov addition of electrophilic palladium(II) would lead to the branched product **13**.[26]

In the current study, we limit ourselves to the parts of the catalytic cycle that are expected to influence the reaction selectivity. We have previously studied the oxidative addition

Scheme 9. Reaction Path Used in Initial Modeling Investigation



in some detail,[27] and the present investigation starts with the oxidative addition complex coordinating a model of the allyl ether **16** (Scheme 9). We concern ourselves only with the simplest aryl, Ph, and chlorides are the only halides considered. Complex **16** undergoes carbopalladation to give intermediate **17**, which must lose the coordination to the phenyl group, yielding key intermediate **18**. Here the reaction branches, eliminating either a benzylic hydrogen through TS **19** to product complex **20**, or an α-ether hydrogen through TS **21** to yield **22**. For each β-elimination, we limit ourselves to the experimentally preferred double-bond geometry; **20** is trans, whereas **22** prefers cis. On the basis of the isotopic labeling studies, we assume that the β-hydride eliminations are effectively irreversible, proceeding with product elimination and base-assisted deprotonation before the product complexes **20** and **22** can revert to **18**. Looking for example at **20**, a reversion from this complex would be expected to give significant amounts of the regioisomer of **18** with Pd bound instead to the benzylic carbon, with concomitant deuterium incorporation on the central allyl carbon; since no such products are observed, we assume that deprotonation from Pd in **20/22** is significantly faster than readdition of palladium hydride to the alkene.

The current reaction is "ligand-free", which simply means that in the absence of specific ligands such as phosphines, any of the species present in solution can potentially act as a ligand. Assuming that ligand exchange is efficient, we are required to investigate all plausible ligand combinations for intermediate **17**, as well as for the competing transition states **19** and **21**. For the first set of experimental conditions to be examined, this includes six combinations of acetate and solvent (formamide, FA[28]). For the second set, we must also consider acetate-free complexes, with chloride as the negatively charged ligand, and

(22) Compound **12j** was prepared via selective hydrogenation of the tetrahydropyranyl derivative of 3-phenyl-2-propyn-1-ol according to the method described by: (a) Denis, J.-N.; Greene, A. E.; Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46–50.

(23) Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5*, 31–44.

(24) (a) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314–321. (b) Kozuch, S.; Amatore, C.; Jutand, A.; Shaik, S. *Organometallics* **2005**, *24*, 2319–2330. (c) Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. *J. Am. Chem. Soc.* **2005**, *127*, 11102–11114.

(25) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558–3563.

(26) Fristrup, P.; Quement, S. L.; Tanner, D.; Norrby, P.-O. *Organometallics* **2004**, *23*, 6160–6165.

(27) (a) Ahlquist, M.; Fristrup, P.; Tanner, D.; Norrby, P.-O. *Organometallics* **2006**, *25*, 20662073. (b) Ahlquist, M.; Norrby, P.-O. *Organometallics* **2007**, *26*, 550–553.

(28) Explicit DMF solvent is modeled by a formamide moiety, FA, and Et_3N is modeled by NH_3. For each complex investigated, we verify that this replacement does not produce any nonphysical hydrogen bonds.

Table 4. Calculated Free Energies of 17 (Scheme 9), with All Ligand Combinations[a]

entry	label	conditions	X	Y	charge	G_{rel} (kJ/mol)
1	**a**	DMF, K_2CO_3, Bu_4NOAc	FA[b]	OAc	0	67
2	**b**		OAc	FA	0	53
3	**c**		OAc	OAc	1−	38
4	**d**			OAc	0	66
5	**e**		OAc		0	22
6	**f**		κ^2-OAc		0	0
7	**g**	DMF, Et_3N, Bu_4NCl	FA	Cl	0	49
8	**h**		Cl	FA	0	32
9	**i**		Cl	Cl	1−	15
10	**j**		Cl	NH_3	0	0
11	**k**		NH_3	Cl	0	2
12	**l**			Cl	0	39
13	**m**		Cl		0	14

[a] The relative free energies within each set are calculated as an equilibrium between any two complexes and free ligands in solution. [b] FA = formamide.

the potential involvement of the amine base (here modeled by NH_3[28]), giving seven additional ligand combinations. The calculated free energies of all ligand combinations for intermediate **17** are given in Table 4.

We should first consider the potential errors in Table 4. All free energies include the gas-phase vibrational contributions, and in particular the entropy is expected to be exaggerated by this treatment, increasing the preference for ligand dissociation. Furthermore, the calculations refer to standard state, that is, 1 M solution of all species. In reality, the solvent concentration is ca. 12 M, increasing the chemical activity of free solvent by almost 10 kJ/mol, whereas for other potential ligands that are present in much lower concentrations, the two effects should partially cancel. Finally, the NH_3 group is probably too small to be an effective model for Et_3N. Visual inspection of complexes containing the NH_3 ligand indicates that "real" amine complexes should be much more crowded. All in all, we estimate that comparisons with complexes containing FA or NH_3 could be in error by up to 20 kJ/mol, but that other relative energies should be accurate to within ca. 10 kJ/mol.

With the potential errors in mind, we can now analyze the results in Table 4 in more detail. Somewhat surprisingly, it seems that, in the presence of excess acetate, **17** shows a preference for a bidentate coordination mode with a single acetate ligand (**17f**). Due to the strong trans effect of the alkyl group, acetate can also disconnect the trans-O to yield **17e** at a cost of only 22 kJ/mol. Other ligand combinations are substantially higher in energy, even accounting for the difference in concentration between acetate and solvent. However, we also note that all complexes are calculated with a continuum model of the solvent, so that the difference between, for example, **17b** and **17e** is only the difference between explicit and implicit solvation treatment. Since the continuum treatment accounts only for the electrostatic interaction, whereas the explicit solvent also includes molecular orbital interaction, the difference between the two types of calculations is surprisingly low.

Looking at the acetate-free complexes, we see that amine coordination is strongly favored, but this result is seriously in doubt due to the neglect of steric repulsion in our model system. The cis-mono-Cl complex **17m** is also very low in energy and would probably be favored over **17j** and **17k** with a more appropriate amine model. We also know from the experimental study that the amine base has very low influence on the selectivity of the reaction (Table 2, compare entries 9 and 10) and that the reaction with only amine and no chloride is extremely slow (Table 2, entry 8). Interestingly enough, the anionic complex with two chloride ligands, **17i**, is also quite low in energy and might easily be formed from oxidative addition from an anionic Pd^0 complex,[24,27] but the value may not be reliable,[29] since it contains the relative continuum solvation energy of compact and diffuse anions.

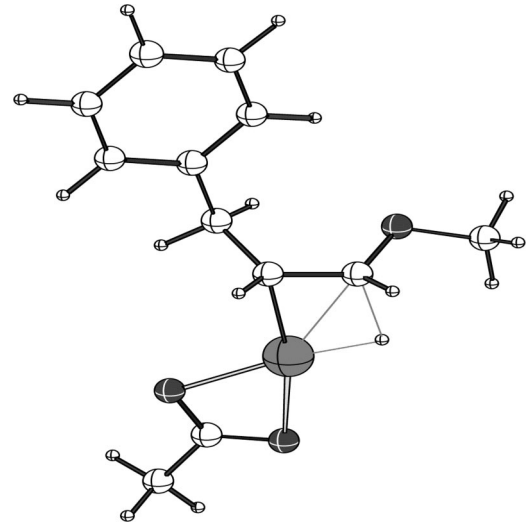


Figure 2. Transition state **21f**.

The deuterium labeling experiment has proven the β-hydride elimination to be irreversible, and hereby the regioselectivity to be kinetically controlled. The distribution of regioisomeric products is therefore expected to be determined by the relative free energy of the two β-hydride elimination transition states **19** and **21**. However, starting from the promising acetate intermediate **17f**, **19f** is disfavored by 20 kJ/mol compared to **21f** (Figure 2), in clear contradiction to the experimentally observed preference for cinnamyl ether product. This prompted us to search for alternative mechanisms.

Previously, it has been reported that acetate coordinated to transition metals is able to accept a proton from a substrate bound to the metal via a cyclic transition state.[30] We located several transition states of this type, depicted in Figure 3, with and without either explicit solvent or the ether side chain coordinated to Pd. The direct proton through-space transfer to a coordinated acetate in a cis position is very unfavorable; **19b** is 139 kJ/mol and **19e** 97 kJ/mol above that of **21f**. More promising is hydrogen-bond assistance from an acetate ligand cis to the hydride-receiving site; **19a** is only 11 kJ/mol higher than **21a**, and **19d** is actually slightly below **21d**. However, each of these four transition states is still ca. 60 kJ/mol higher than **21f**, which remains the globally preferred TS.

We next investigated whether the erroneous selectivity prediction could be the result of using an insufficient level of theory. Transition states **19f** and **21f** were reoptimized using a triple-ζ basis set with diffuse functions, also at the LMP2 level, with and without continuum solvent. The results, shown in Table 5, clearly indicate no significant change.

At this point, the inconsistency between the experimental results and the calculations indicated to us that a more thorough investigation of the mechanistic details for the entire reaction pathway was necessary. We realized that complex **17**, the immediate product from the carbopalladation step, is predisposed for elimination of the benzylic hydrogens. It is not possible to

(29) Ahlquist, M.; Kozuch, S.; Shaik, S.; Tanner, D.; Norrby, P.-O. *Organometallics* **2006**, *25*, 45–47.
(30) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754–3755.

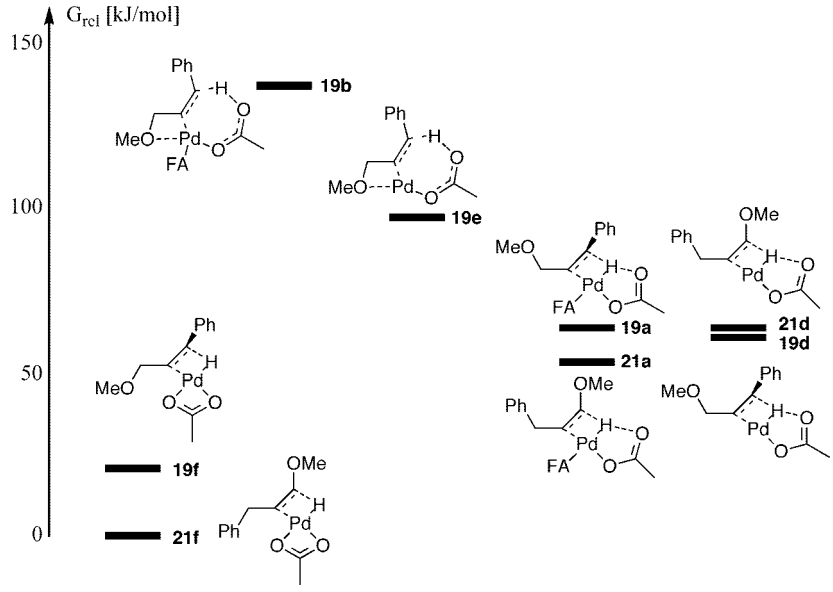
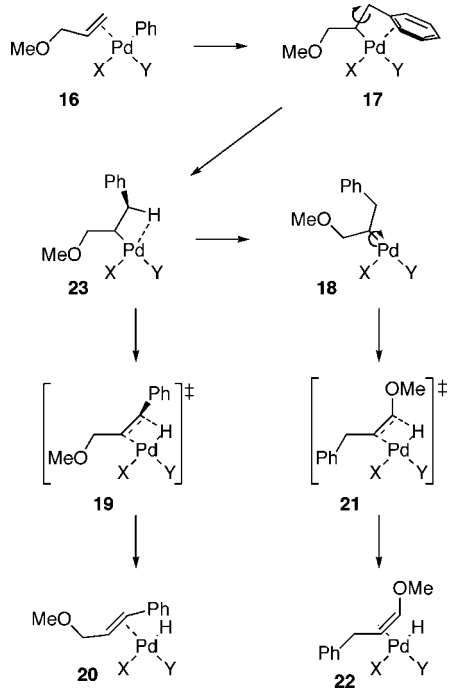


Figure 3. Alternative forms of transition states **19** and **21**.

Table 5. Potential Energy Difference between 19f and 21f at Different Levels of Theory

method	basis set	solvation	$\Delta\Delta E^{\ddagger}$ (kJ/mol)
B3LYP	LACVP*	none	12
B3LYP	LACVP*	DMF	14
B3LYP	LACV3P**++	none	12
B3LYP	LACV3P**++	DMF	14
LMP2	LACV3P**++	none	13
LMP2	LACV3P**++	DMF	16

Scheme 10. Detailed Reaction Path



rotate the C−C bond in **17** to form **18** without first passing through the relatively stable agostic complex **23**. However, it is apparent that **23** can reach **19** without first passing through **18** (Scheme 10).

Complex **18** is very labile and is flanked by additional bond rotation transition states only marginally higher in energy than **18** (by ca. 1 kJ/mol). On the free energy surface, **18** is higher than **21** for many ligand combinations, with the result that we no longer have a Curtin−Hammett situation. The branching of the reaction path is determined by the relative energy of **19** and **18**: not, as originally assumed, by the competition between **19** and **21**. Thus, the selectivity is determined by a limiting rotation around a single bond, a rare phenomenon.

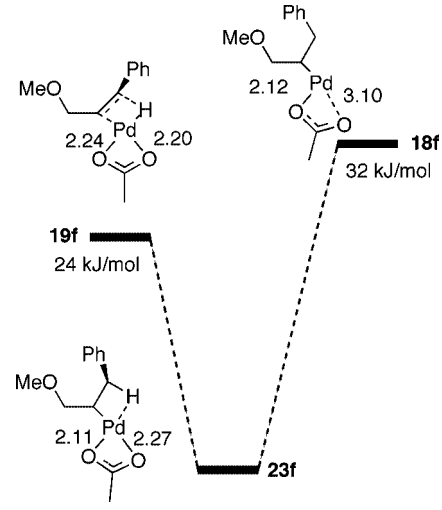


Figure 4. Branching from **23f**, through either **19f** or **18f**.

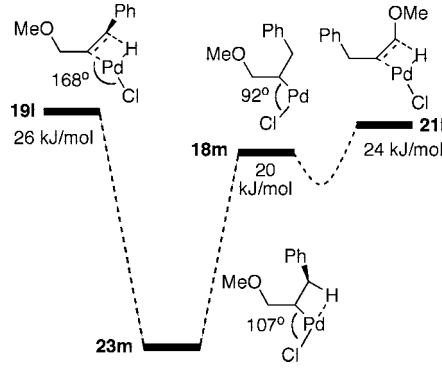


Figure 5. Branching from **23m**, either through **19l** or through **18m** followed by **21l**.

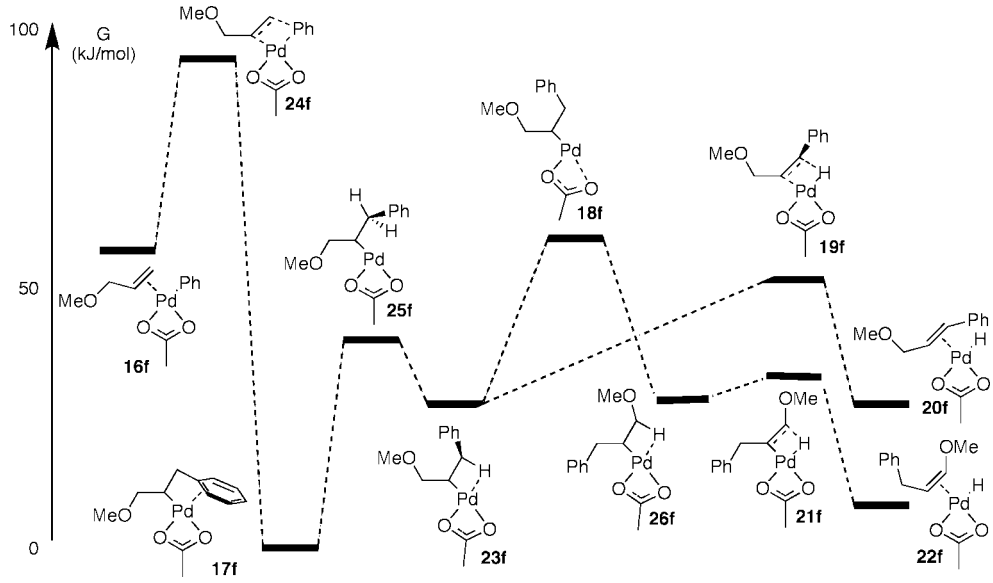


Figure 6. Free energy profile with an acetate coordinating to palladium.

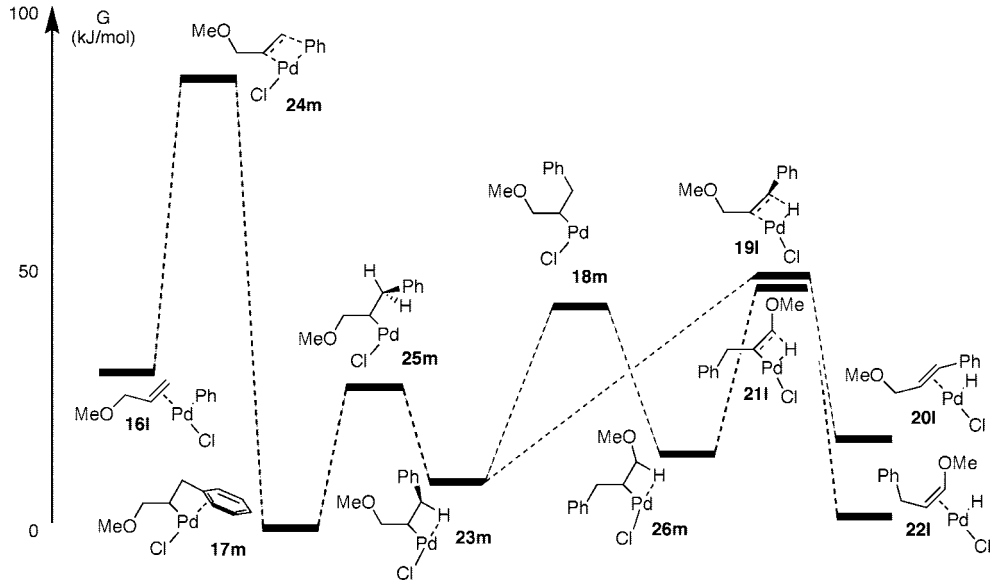


Figure 7. Free energy profile with a chloride coordinating to palladium.

Figure 4 shows the branching from acetate complex **23f**; transition state **19f** leading to the observed cinnamyl product is clearly preferred over the longer path through **18f**. The energy difference, 8 kJ/mol, is very close to the experimentally observed difference of 6 kJ/mol. Such a good agreement is surprising, and probably fortuitous, considering that we are comparing barriers of fairly different types. Looking in more detail at the structures, we can see that the acetate ligand in bidentate mode has the ability to partially accommodate the severe change in trans influence occurring in this reaction. Both an alkyl and a hydride are expected to have very strong trans influences, but in **19f**, neither is fully developed, leading to a symmetric bidentate binding mode. In **18f**, the strong trans influence of the alkyl leads to a drastic elongation of one Pd−O bond; the acetate has virtually been forced into a monodentate binding mode, with concomitant increase in energy (cf. Table 4, entries 4−6).

When the bidentate acetate ligand is replaced by a monodentate chloride, the picture changes; the chloride position is very labile. By using its lone pair to fill a neighboring empty coordination site, the chloride automatically switches position to avoid large trans influences. Thus, elongating the C−H bond in complex **23m** to generate the β-hydride elimination TS **19** in fact yields **19l**, whereas breaking the agostic bond by C−C rotation leads to **18m**, which then passes through another agostic complex to the alternative β-hydride elimination TS **21l**, which in this case is higher than **18m** (Figure 5). Interestingly, we are now almost back to a Curtin−Hammett situation, with the product selectivity being largely controlled by the competition between **19l** and **21l**, but the necessity of passing through several preceding bond rotations will slow down the passage through **21l**. The selectivity in a case such as this is expected to be poor, as is indeed observed in the corresponding experiment (ca. 2:1). The proposed "acetate effect", favoring cinnamyl products, can now be rationalized from a comparison of these two systems. The ability of acetate ion to act as a bidentate ligand has a stabilizing effect along most of the reaction path, except for **18**, where the very strong trans effect of the alkyl group forces the acetate into what is essentially a monodentate binding mode, making **18** the highest energy structure after the selectivity branching point. On the other hand, the chloride ligand has an

effect that is more equal over the entire reaction path, so that the influence of the necessary passage through complex **18** is minimized.

To complete the selectivity picture, we have calculated all steps of the reaction path depicted in Scheme 9 for the energetically most favorable systems with and without acetate: that is, starting from **16f** or **16l**. The resulting free energy surface for the system with acetate coordinating to palladium is shown in Figure 6. We see that the carbopalladation step (TS **24f**) is not rate limiting but is definitely irreversible, as expected under catalytic conditions.[31] From the resulting intermediate **17f**, there is a moderate barrier for breaking the coordination to the aryl and rotating to the first agostic complex, **23f**. At this branching point, a direct β-elimination through **19f** leads to complex **20f**, which yields the observed major product. Choosing instead a series of bond rotations leads through the high-energy intermediate **18f**, which proceeds to the second agostic complex, **25f**, which can undergo β-elimination through **21f** to the complex **22f**. It is clear that the selectivity is kinetic in origin, since the complex of the observed minor product **22f** is substantially below the complex of the major product **20f** in free energy.

The free energy profile for the system where the acetate has been replaced by a monodentate chloride can be seen in Figure 7. The differences compared to Figure 6 are minor, but significant. The bond rotation path from **23m** to **26m** is lower in energy and is no longer limiting; the (low) selectivity is still entirely kinetic in origin and is mainly a result of the competition between the two β-elimination transition states, as originally assumed. The path leading to the enol ether product is calculated to be slightly favored. We know from experiment that this preference should actually be reversed, since the observed 2:1 distribution of cinnamyl and enol ether indicates an energy difference of 2 kJ/mol in favor of the former, a difference that is probably similar to the accuracy of the methods employed herein. The trend that replacement of acetate with chloride results in lower regioselectivity is nevertheless clear.

Conclusions

We have demonstrated that acetate anions can influence the selectivity of the syn-β elimination of HPdX species in the Heck reaction of aryl iodides and bromides with allyl alcohol derivatives. This effect has been used to develop an experimentally straightforward and synthetically useful route to the synthesis of cinnamyl alcohol derivatives using $Pd(OAc)_2$ as precursor of Pd(0) species under phosphine-free conditions. The reaction tolerates a variety of functional groups, including ether, amide, alcohol, aldehyde, ketone, ester, cyano, carboxylic acid, and nitro groups, and compares well with known palladium-catalyzed processes. We have also shown that the selectivity observed in forming the vinylic substitution products is kinetic in origin under the conditions used.

Furthermore, the DFT study indicates that, when discussing the β-elimination regioselectivity of the Heck reaction, it is not sufficient to investigate the different β-hydride elimination transition states. Very interestingly, it was found that the rotation of a single bond to break an agostic interaction in the intermediate is a high-energy process. Under certain conditions this single bond rotation has a higher barrier than β-hydride elimination and is thus selectivity determining. Thus, we have uncovered a selectivity source that to our knowledge has very few precedents[32] but which could be of importance in many other reactions involving alkyl−metal intermediates.

We have found that the trans effect plays an important role in determining the preferred positions of ligands in the reaction intermediates and transition states, and for this reason the regioselectivity is very dependent on the type of ligand coordinated to palladium. In particular, the experimentally observed "acetate effect" could be explained by the ability of acetate to coordinate to palladium in a bidentate fashion.

Finally, as we also noted in earlier studies,[33] we have found the use of solvated free energy values to be extremely important for the description of the reaction path. On any energy surface ignoring either solvation or vibrational contributions to the free energy, even when including a coordinating solvent molecule, the selectivity is determined by the competing β-elimination transition state. The experimentally observed regioselectivity can be reproduced only when both thermodynamic contributions and continuum solvation are included in the calculated free energies.

Computational Details

All calculations have been performed using Jaguar, version 6.5 release 106.[34] We have used the B3LYP hybrid functional[35] together with the basis set LACVP*[36] (except where otherwise mentioned). All complexes have been optimized first in the gas phase and then in solvent, modeled by a Poisson−Boltzmann self-consistent reaction field (PB-SCRF)[37]with parameters suitable for DMF (dielectricity constant, epsout = 38; probe radius, radprb = 2.47982). In all cases, the gas-phase and solution geometries are very similar. Vibrational analysis using the analytic Hessian has been performed for the gas-phase geometries only. Final free energies (G_{sol}) were obtained by adding the thermodynamic contributions determined in the gas phase (at 363.15 K) to the final energies obtained for the very similar geometries in solution.

Acknowledgment. Work was carried out in the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica and by the University "La Sapienza". The Center for Sustainable and Green Chemistry is sponsored by the Danish National Research Foundation for the period 2005−2010. P.-O.N. is grateful to the Swedish Research Council for support.

Supporting Information Available: A complete description of experimental details and product characterization data and tables with modeling results in the form of Cartesian coordinates and absolute energies of calculated geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

OM800114A

(31) It has recently been suggested that under base-free, stoichiometric conditions, the carbopalladation step could become reversible: Amatore, C.; Godin, B.; Jutand, A.; Lemaître, F. *Organometallics* **2007**, *26*, 17571761. In the absence of a base-induced forward reaction, the barrier to the reverse reaction calculated herein would not be insurmountable.

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