Amination of π-Allylpalladium Chloride Complexes. A Mechanistic Study

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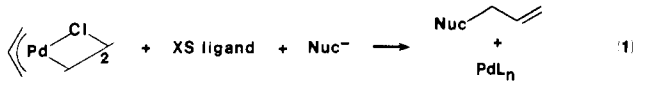
Abstract: Conductivity measurements indicate that the reaction of π-allylpalladium chloride complexes with excess phosphine in THF does not generate cationic π-allylpalladium complexes. Rather, dynamic σ-allylpalladium complexes are formed. The reaction of neutral π-allylpalladium chloride complexes with excess phosphine and dimethylamine was compared and contrasted with the same reaction involving preformed cationic π-allylpalladium complexes, and a change in mechanism was proposed.

Since the initial observation of Tsuji[2] that π-allylpalladium halide complexes will react with nucleophiles in the presence of strongly coordinating ligands (or solvents), this reaction (eq 1)

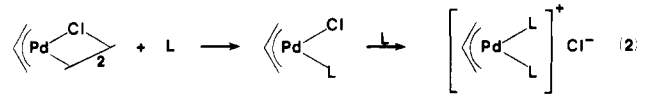


(1)

has found extensive application in organic synthesis. Stabilized carbanions[3] and amines[4,5] have been most extensively studied as nucleophiles, and natural products ranging from humulene[6] to ibogamine[7] have been synthesized by using nucleophilic attack on a π-allylpalladium complex as the key step. The development by Trost[8] of catalytic alkylation and amination of allyl acetates based on this same chemistry has further broadened the application of this reaction to organic synthesis. Although cationic species, resulting from displacement of a chloride by the added ligand, have been claimed to be the reactive species in these reactions, this has not been unequivocally demonstrated. Since our studies[4] of the reaction of π-crotylpalladium chloride with dimethylamine in THF show significant differences between reactions for which cationic species are clearly involved (addition of $AgBF_4$) and those involving supposed generation of cationic species only by the addition of excess ligand, a systematic study of the role of cationic intermediates in nucleophilic attack on π-allylpalladium halide complexes was carried out.

Results and Discussion

If charged species are important intermediates in a reaction, they should, in principle, be detected by conductivity measurements. Indeed, conductimetric studies of the reaction of π-allylpalladium halides with tertiary phosphines in 20% v/v aqueous acetone solvent showed that the first equivalent of phosphine resulted in bridge splitting of the monomer, with no increase in conductivity, while the second equivalent formed an ionic complex, with a substantial increase in conductivity (to an ultimate value of $\sim 10^{-4}\ \Omega^{-1}$) (eq 2).[9] Cationic π-allylpalladium complexes **1**–**3**,



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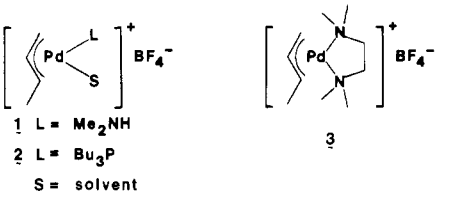
formed from the halo-bridged dimer by the precipitation of



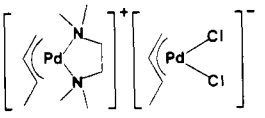
1 L = Me_2NH
2 L = Bu_3P
S = solvent

3

chloride by silver, show similar conductivities in both acetone and THF. Thus conductance affords a good probe for the presence of cationic π-allylpalladium complexes.

Most reactions of nucleophiles with π-allylpalladium halide complexes have been carried out by the simple addition of excess ligand and nucleophile to the complex in the nonpolar (relative to aqueous acetone) solvent, THF. Thus it was of interest to monitor the conductance of THF solutions of π-crotylpalladium chloride upon treatment with increasing amounts of phosphine or amine. If cationic complexes are formed in these solutions, increased conductivity should be noted. To our surprise, addition of 3 equiv (per Pd) of tri-*n*-butylphosphine to a THF solution of π-crotylpalladium chloride led to *no* change in conductivity indicating that no detectable formation of ionic intermediates in this less polar solvent had occurred. Similar results were obtained by using dimethylamine in place of the phosphine. In spite of this, π-allylpalladium chloride undergoes amination in high yield when treated with an amine and 3 equiv of tri-*n*-butylphosphine (see below). Thus the role of ionic species in these reactions is suspect.

To see if more strongly coordinating ligands could form ionic complexes in THF, π-crotylpalladium chloride was treated with tetramethylethylenediamine (TMEDA), and the conductance was monitored (Figure 1). Contrary to expectation, the conductance increased steadily until 0.5 equiv of TMEDA/Pd had been added and then remained constant over the addition of up to 2 equiv of TMEDA/Pd. Thus complete displacement of Cl^- to form complex **3** (with Cl^- as a counterion) did *not* occur in THF. Rather the complex ion pair **4** was isolated in quantitative yield. Apparently



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THF lacks sufficient polarity to stabilize the simple ion pair with chloride as the anion.[10]

The structure of **4** was unequivocally determined from a high-field (360 MHz) NMR study, which demonstrated the presence of two different π-allyl ligands, which exchange rapidly at +20 °C. A single-crystal X-ray diffraction study confirmed the assigned structure and is reported elsewhere.[11] Although complex ion pairs such as **4** are not directly involved in nucleophilic attack on π-allylpalladium complexes, the related π-olefin complex

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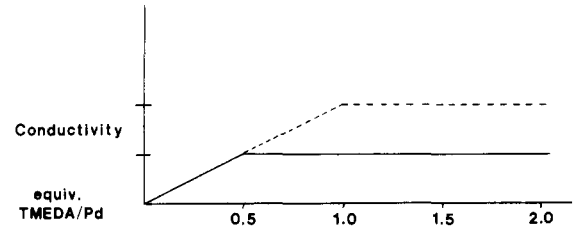


Figure 1.

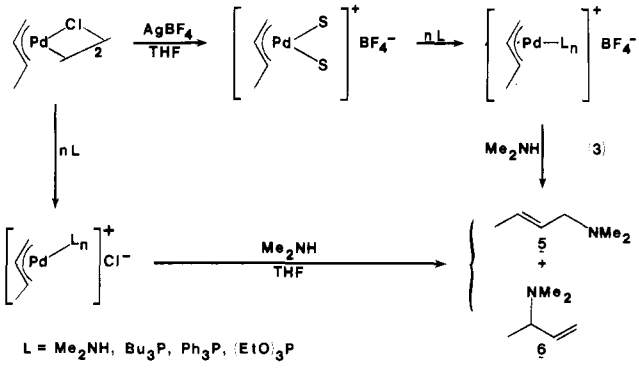
Table I. Reactions of [π-Crotylpalladium(L_n)]$^+BF_4^-$ with Dimethylamine (10 equiv)

equiv[a] (ligand)	time	$CH_3CH(NMe_2)$-$CH{=}CH_2$, % yield[b]	$CH_3CH{=}CHCH_2NMe_2$, % yield[b]	% yield Σ
(1)	3 h	2	64	66
	22 h		76	76
(2) 1 (Bu_3P)	3 h	1	46	47
	21 h		41	41
(3) 2 (Bu_3P)	3 min		32	32
	9 h		54	54
(4) 4 (Bu_3P)	7 h	4	26	30
(5) 1 (Ph_3P)	2 min	23	70	93
	9 h	23	81	100
1 (Ph_3P)[c]		3	46	49
(6) 2 (Ph_3P)[c]	18 min	10	94	100
(6') 2 (Ph_3P)[c]		<1	63	64
(7) 4 (Ph_3P)	3 h	12	38	50
	36 h	4	60	64
(8) 1 [$(EtO)_3P$]	3 min	17	72	89
	11 min	4	93	97
(9) 2 [$(EtO)_3P$]	2 min	7	73	80
	10 min	6	82	88
(10) 4 [$(EtO)_3P$]	3 min	21	67	88
	13 min	29	56	85
(11) 1 (TMEDA)	8 min		6	6
	40 min		24	25
	6 h		28	28

[a] Equivalents based on Pd. [b] Yields are calculated by comparison of peak areas of product amines to those of an internal standard. [c] These are yields for isolated, purified material.

ion pairs are of central importance in the reactions of nucleophiles with π-olefin palladium complexes. This topic will be the subject of a forthcoming report from these laboratories.

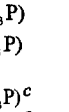
Having shown that simple cationic π-allylpalladium complexes are *not* formed in THF upon reaction with excess ligand, it remained to investigate the differences, if any, between allylic aminations in the presence of excess ligand and those clearly involving cationic π-allyl complexes. To this end the reactions described in eq 3 were carried out, and the results are collected in Tables I and II.



(3)

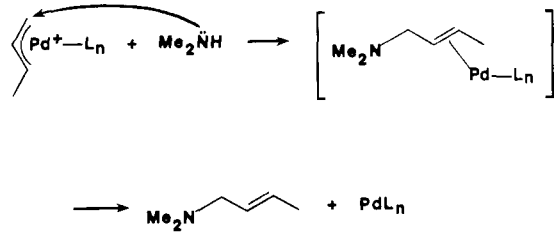
To study the reactivity of dimethylamine toward cationic π-allylpalladium complexes in THF, we treated π-crotylpalladium chloride with $AgBF_4$ and removed the resulting AgCl by filtration. Ligand and dimethylamine were then added, and the production of the isomeric allylamines was followed by GC (Table I). With no added ligand (excess dimethylamine will act as a ligand) the amination was slow, but ultimately produced a reasonable yield of allylamine, which was overwhelmingly the terminal amine resulting from attack at the unsubstituted allylic terminus. With 1, 2, and 4 equiv of added tri-*n*-butylphosphine (a strong σ donor ligand), the reaction was initially faster than that with amine alone, but only 50% conversion was noted. With 4 equiv of Bu_3P, the reaction was slower than that with 2 equiv. Again, the terminal amine was formed almost exclusively. With added triphenylphosphine (a weaker σ donor) the reaction was very fast with 1 or 2 equiv of phosphine, and significantly slower with 4 equiv. The same results were obtained by using the weak donor, $(EtO)_3P$. In all cases with the cationic complexes by far the major product was the terminal allylamine, from attack at the less substituted allylic terminus.

Table II. Reactions of [π-Crotylpalladium chloride]$_2$ with Dimethylamine (10 equiv)

equiv[a] (ligand)	time	$CH_3CH(NMe_2)$-$CH{=}CH_2$, % yield[b]	$CH_3CH{=}CHCH_2NMe_2$, % yield[b]	% yield Σ
(1)	3 min	12	19	31
	19 h	8	22	30
(2) 1 (Bu_3P)	12 min	21	8	29
	90 min	32	10	42
	44 h	1.7	55	57
(3) 2 (Bu_3P)	14 min	28	12	40
	95 min	15	40	55
	7 h	4	61	65
(4) 4 (Bu_3P)	6 min	75	25	100
	23 h	20	80	100
(5) 1 (Ph_3P)	3 min	50	4	54
	39 h	21	51	72
(6) 2 (Ph_3P)	4 min	71	22	93
	39 h	22	78	100
(6') 2 (Ph_3P)[c]		46	12	58
(7) 4 (Ph_3P)	55 min	55	32	87
	24 h	57	39	96
4 (Ph_3P)[c]		80	20	100
(8) 	3 min	48	34	82
	90 min	24	78	100

[a] Equivalents based on Pd. [b] Yields are calculated by comparison of peak areas of product amines to those of an internal standard. [c] These are yields for isolated, purified material.

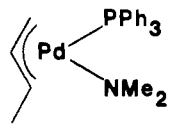
These results are consistent with a mechanism in which the nucleophile attacks a cationic π-allylpalladium complex coordinating to one or more ligands (eq 4). The "more" cationic the



(4)

complex, the more prone to nucleophilic attack (formal gain of 2 e^-) it should be. Thus, strong donor ligands such as Me_2NH, TMEDA, and *n*-Bu_3P actually slow the reaction relative to weaker donors such as Ph_3P and $(EtO)_3P$. The added ligand also must stabilize the Pd(0) complex resulting from nucleophilic attack. Thus, the net effect of the nature of the phosphine on the amination of π-allylpalladium complexes surely depends on the phosphine's ability to perform both functions. External nucleophilic attack (without prior coordination) is involved here, based both on previous published results[12] and on the observation that

the preformed complex, **7**, did not produce allylamines under the amination conditions.



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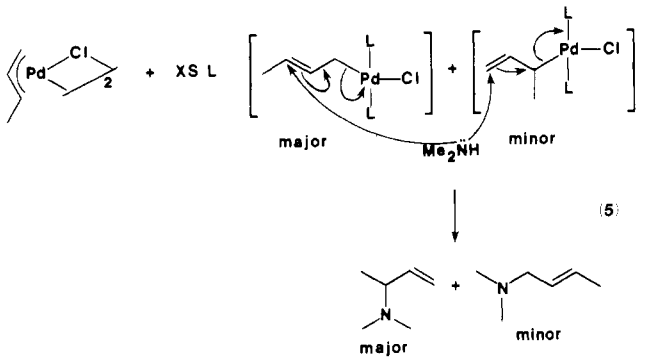
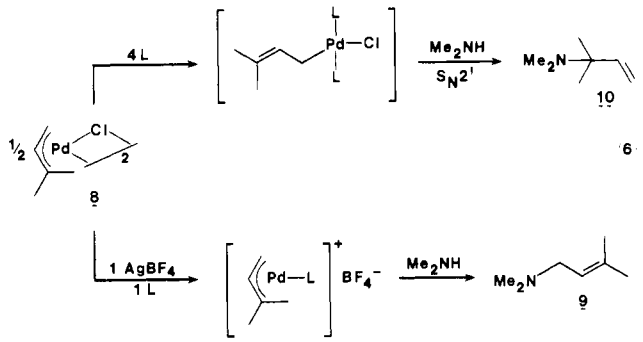
This series of experiments was compared to a similar series in which cationic complexes were *not* generated, but rather, varying amounts of phosphine were added to the π-allylpalladium chloride itself. (Recall that this resulted in *no* change in conductivity in THF, indicating the lack of significant concentrations of ionic complexes.) These results are collected in Table II. Under these conditions, optimum yields and rates were obtained when 4 equiv of phosphine were used. Tri-*n*-butylphosphine, triphenylphosphine, and diphos were equally efficient. *In marked contrast to the cationic complexes, the major regioisomer of the amine formed was the internal isomer rather than the terminal isomer.* This complete reversal of regiochemistry, coupled with the observed absence of ionic species in these systems, strongly argues for a change in mechanism on going from the cationic to the neutral complex. (It should be noted that the internal amine isomer slowly rearranged to the terminal isomer upon prolonged contact with the reaction mixture, so these yields of internal isomer reported are the minimum possible yields.) It is proposed that amination of π-crotylpalladium chloride complexes solely in the presence of excess ligand does *not* involve cationic π-allylpalladium complex intermediates, but rather involves an S_N2' amination of the corresponding σ-allylpalladium complex, as shown in eq 5.



Numerous NMR studies[13,14] in several relatively nonpolar solvents show that, in the presence of phosphine, π-allylpalladium chloride complexes are converted to (dynamic) σ-allyl complexes as in eq 5. Since σ-allylpalladium complexes are clearly present with excess phosphine, they are likely reactive intermediates for nucleophilic attack. With unsymmetrical allyl groups, the major σ-allyl complex formed is that corresponding to the palladium occupying the *least* substituted allylic carbon.[13] S_N2' attack of these σ-allyl complexes should then lead to a mixture of products roughly corresponding to the mixture of σ-allyl complexes present. As seen in Table II, for the π-crotyl complex, the major amination product *does* indeed correspond to an S_N2' attack on the major σ-allyl complex present. That S_N2' rather than S_N2 attack on the σ-allyl complex occurs is likely to be due to the extreme size of the leaving group $(R_3P)_2PdCl$, which severely hinders nucleophilic attack at the Pd-bearing carbon, and diverts the nucleophile to the much more sterically accessible 3 position of the allyl system. Reactions proceeding by this mechanism should be less sensitive to the nature of the ligand than those going via a cationic π-allyl PdL_2 complex because the site undergoing nucleophilic attack is insulated from the metal by a CH_2 group in the former case. This is indeed the observation. For the S_N2' mechanism the ligand acts solely to generate the σ-allyl complex and to stabilize the Pd(0) leaving group. For the mechanism involving cationic π-allyl PdL_2 complexes, the nature of the phosphine has a direct effect on the electron density in the π-allyl system undergoing nucleophilic attack.

To further test the role of S_N2' reactions of π-allylpalladium complexes, the 1,1-dimethylallylpalladium chloride complex, **8**, was synthesized. NMR studies of this complex show that in the presence of triphenylphosphine in a ratio >2 PPh_3/Pd, this complex exists as a σ-allyl system in which the palladium occupies the *primary* carbon to at least 80%.[13] Hence, reaction of this π-allyl complex with Me_2NH by an S_N2' mechanism should lead predominantly to amination at the tertiary carbon. Indeed, it does. Reaction of π-(1,1-dimethylallyl)palladium chloride with dimethylamine and 4 equiv of Ph_3P in THF led to exclusive amination of the tertiary carbon of the allyl system (eq 6). In



contrast, reaction of the same π-allylpalladium complex with 1 equiv of $AgBF_4$ to form the cationic π-allyl complex, followed by 1 equiv of Ph_3P and excess dimethylamine, led to exclusive amination at the primary carbon of the allylic system. This complete reversal of regioselectivity not only argues for a change in mechanism, if general, it offers a practical and useful procedure to control the site of attack on π-allylpalladium complexes.

Perhaps the most compelling evidence for the proposed change in mechanism comes from a comparison of entry 6′ in Table I with entry 6′ in Table II. If the reaction of π-allylpalladium chloride with dimethylamine in the presence of excess phosphine proceeded through a cationic π-allyl complex as shown in eq 1, the *only difference* between these two experiments would be the counterion. That is, in Table I, one would have $[(\pi\text{-crotyl})PdL_2]^+BF_4^-$, and in Table II $[(\pi\text{-crotyl})PdL_2]^+Cl^-$. However, in the BF_4^- case the regioselectivity of nucleophilic attack is >99% in favor of attack at the primary carbon of the allyl system, whereas with Cl^-, the regioselectivity is exactly the opposite, ~20:80 (primary vs. secondary). This seems, to us, to be too great a difference to be due solely to the nature of the counterion in a π-allylpalladium L_2 cation. Hence, a difference in mechanism is proposed.

A wide variety of other palladium-assisted allylic aminations and alkylations have been reported. The regioselectivities of these reactions show remarkable variations with experimental conditions, and are often rather difficult to rationalize only in terms of a cationic π-allylpalladium intermediate. In view of the results reported herein, the possibility exists that these variations are due to changes in the mechanism of the reaction, rather than to more subtle and obscure steric, electronic, or other effects.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer 421 spectrometer and mass spectra on an LKB 9000 spectrometer. GLC was performed on a Varian Aerograph 1400, using 20% Apiezon L on Chromosorb W containing 10% potassium hydroxide as the stationary phase.

Materials. Methylene chloride, chloroform, and acetone were reagent grade and used as received. Tetrahydrofuran (THF) was purified by distillation from potassium–benzophenone. Acetone-d_6 and THF-d_8 (99%, Stohler Isotope Chemicals) were used as received. Tetrabutylammonium chloride, tetrabutylammonium bromide, and tetrabutylammonium fluoroborate were gift samples from Bofors Nobel Kemi.

π-Crotylpalladium chloride was prepared by a modification of a published procedure.[15] Sodium tetrachloropalladate (8.238 g, 28 mmol)

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(13) J. Powell and B. L. Shaw, *J. Chem. Soc. A*, 1839 (1967).
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Table III. Conductivity of π-Crotylpalladium Complexes (0.5–1.0 M Solutions in THF)

compd	equiv added ligands/Pd (ligand)	temp, °C	conductivity, $cm^2\ \Omega^{-1}\ mol^{-1}$
Bu_4NCl		25	3.4
Bu_4NCl		−50	2.3
Bu_4NBr		25	1.7
Bu_4NBr		−50	0.55
Bu_4NBF_4		25	6.2
Bu_4NBF_4		−50	2.7
4		25	1.6
4		−50	0.5
		25	6.0
	1 (PPh_3)	25	7.2
	1 (PPh_3)	25	0.008
	2 (PPh_3)	25	0.01
	4 (PPh_3)	25	0.025
	4 (PPh_3) + 1 (Me_2NH)	25	0.05
	1–4 (Bu_4P)	25	0
	1 (TMEDA)	−50	30.5[a]

[a] Value in acetone.

was dissolved in methanol (250 mL) and cooled to 0 °C and tin(II) chloride was added to the red-brown solution. After 5 min 3-chlorobutene-1 was added and a yellow precipitate slowly formed. Stirring was continued for 1 h, the reaction mixture was poured onto crushed ice and extracted with chloroform, and the chloroform was washed with water and dried over calcium chloride. The solvent was removed at room temperature and the residue dried under reduced pressure to give 5.1 g (92%) of light-lemon-colored crystals which were further purified by recrystallization from methylene chloride–pentane.

π-Crotylpalladium tetrafluoroborate was prepared in situ.[16] π-3-Methylbutenylpalladium was prepared by a published procedure.[17] The ion pair **4** was prepared by adding *N,N,N',N'*-tetramethyl-1,2-diaminoethane (TMEDA, 227 μL, 1.5 mmol) to a solution of π-crotylpalladium chloride (0.591 g, 3 mmol of palladium) in THF (20 mL). The solvent was evaporated to give light-yellow crystals (0.753 g, 98%) of the ion pair **4**.

N,N-Dimethyl-2-buten-2-amine and *N,N*-dimethyl-2-buten-1-amine (dimethylcrotylamine) were prepared according to Young.[18]

Conductometric Measurements. The data were collected with a model LBR instrument from WTW, Wellheim, Germany, using a Philips PR9510 cell. In the general procedure, the appropriate compound, 0.5 or 1 mmol, was dissolved in the solvent (10 mL) and the conductivity measured at the appropriate temperature, generally 25 or −50 °C. The results are presented in Table III. The influence of the ligands was determined by introducing the ligand, either pure or as a concentrated solution in the appropriate solvent, to the π-allylpalladium complex with a syringe in portions of 0.1 equiv per palladium. After each addition, the solution was allowed to equilibrate. In the reaction of π-crotylpalladium chloride with TMEDA in THF, an essentially linear increase in the conductivity was observed until 0.5 equiv of TMEDA per palladium had been added. The conductivity then remained constant. In contrast, when chloroform or acetone were used as solvent, the conductivity increased until 1 equiv of TMEDA per palladium had been added.

Amination Reactions of π-Crotylpalladium Complexes. Cationic Complexes. π-Crotylpalladium chloride (197 mg, 1 mmol of palladium) was dissolved in THF (5 mL) and silver tetrafluoroborate (195 mg, 1 mmol) dissolved in THF (2 mL) was added with stirring. Silver chloride immediately precipitated and was removed after 5 min by filtration in an open filter funnel. The light-yellow solution was transferred into a closed vessel and reacted under nitrogen atmosphere with the appropriate ligand and an excess of dimethylamine (5–10 mmol) dissolved in THF.

When phosphine ligands were used the formation of the amines **5** and **6** was very rapid. The yields under different conditions are given in Table I.

Neutral Complexes. π-Crotylpalladium chloride (197 mg, 1 mmol of palladium) was dissolved in THF (5 mL) and the appropriate ligand dissolved in THF (2 mL) was added, followed by an excess of dimethylamine (5–10 mmol). Mixtures of the two isomeric amines **5** and **6** were again formed (Table II).

In both procedures, the yields of the amines **5** and **6** were determined either by GC directly or after isolation of the amine fraction by extraction.

π-3-Methylbutenylpalladium Complexes. Cationic Complex. π-3-Methylbutenylpalladium chloride was reacted according to the procedure for the cationic complex of the π-crotylpalladium complex with 1 mol of triphenylphosphine added per mol of palladium. Isolation by extraction and evaporation of the solvent through a short column gave the terminal amine **9**, contaminated by some solvent THF, as the exclusive product (>95% by NMR). NMR ($CDCl_3$) δ 1.8 (s, 3, CH_3), 1.9 (s, 3, CH_3), 2.2 (s, 6, NCH_3), 2.85 (d, J = 8 Hz, 2, $CH_2C{=}C$), 5.3 (t, J = 8 Hz, 1, $C{=}CH$).

When the same procedure was used with the exception that 2 mol of phosphine were added as ligand, the internal amine **10** was obtained as the major product (>90%).

Neutral Complex. π-3-Methylbutenylpalladium chloride was reacted according to the procedure for neutral complex of the π-crotylpalladium complex with 4 mol of triphenylphosphine added per mol of palladium. Extraction gave the internal amine **10** as the exclusive product (>95% by NMR). NMR ($CDCl_3$) δ 1.20 (s, 6, CH_3), 2.2 (s, 6, NCH_3), 4.9–5.1 (m, 2, $CH_2{=}CH$), 5.9 (dd, J = 7, 18 Hz, 1, $CH{=}CH_2$).

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