Palladium(0)-Catalyzed Allylic Aminations: Kinetics and Mechanism of the Reaction of Secondary Amines with Cationic $[(\eta^3\text{-allyl})PdL_2]^+$ Complexes†

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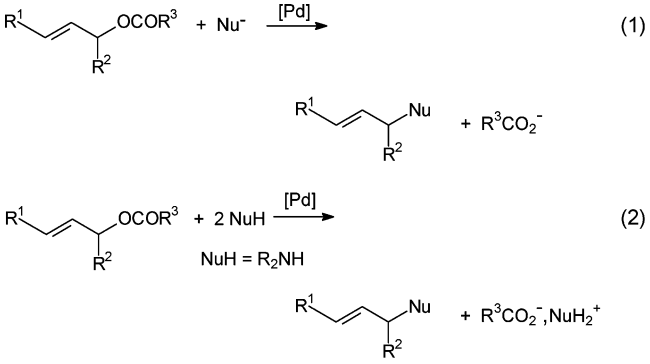
The mechanism of the reaction of secondary amines (piperidine, morpholine) with the cationic complexes $[(\eta^3\text{-PhCHCHCHR})PdL_2]^+BF_4^-$ (R = Ph, L = PPh_3 or L_2 = dppb; R = H, L_2 = dppb) has been investigated in DMF. The reaction, which affords the tertiary allylic amine, is irreversible when L is a monodentate ligand such as PPh_3, whereas the reaction is reversible when L_2 is a bidentate ligand such as dppb. In all cases, piperidine is more reactive than morpholine. The rate and equilibrium constants have been determined in DMF. These results can be combined with our previous results on the mechanism of the reversible formation of cationic $[(\eta^3\text{-PhCHCHCHPh})PdL_2]^+AcO^-$ by reacting Pd^0L_2 complexes with (*E*)-PhCH═CHCH(Ph)OAc. Fully established catalytic cycles are now proposed for the Pd-catalyzed allylic amination of (*E*)-PhCH═CHCH(Ph)OAc by piperidine and morpholine. The amine and AcO^- are in competition in their reaction with the cationic complexes $[(\eta^3\text{-PhCHCHCHPh})PdL_2]^+$. The nucleophilic attack of the amine may be faster than the attack of AcO^- and thus limited by the ionization step in which $[(\eta^3\text{-PhCHCHCHPh})PdL_2]^+$ is formed, this ionization step being turnover limiting for the catalytic cycle.

Introduction

The mechanism of the palladium-catalyzed nucleophilic allylic substitutions has been extensively studied (Scheme 1).[1−3]

Kinetic data on the first steps of the catalytic cycles, i.e., the oxidative addition of Pd^0L_2 (L = monodentate phosphines or L_2 = bisphosphine) with allylic acetates[2] or carbonates,[3] are now available and the cationic complexes $(\eta^3\text{-allyl})PdL_2^+$ formed in the oxidative addition have been well characterized.[2,3]

Scheme 1



Kinetic data on the further step, i.e., nucleophilic attack on $(\eta^3\text{-allyl})PdL_2^+$ complexes, are more scarce. Uguagliati et al.[4] and Crociani et al.[5] have investigated the reaction of secondary amines with cationic $[(\eta^3\text{-}CH_2CHCH_2)Pd(N,N)]^+$ and $[(\eta^3\text{-}CH_2\text{-}CHCH_2)Pd(P,N)]^+$, respectively. In both cases, the secondary amines were found to attack in parallel the η^3-allyl ligand in an

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† This work is dedicated to our friend, the late Professor Marcial Moreno-Mañas.

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irreversible reaction and the Pd^{II} center by reversible coordination. Canovese et al. have investigated the reaction of secondary amines with cationic $[(\eta^3\text{-}CH_2CHCH_2)Pd]^+$ ligated by terdentate S-N-S, N-S-N, N-N-N, and P-N-N ligands, and a parallel attack was also observed.[6] As far as monophosphine ligands are concerned, secondary amines were found to only attack the allyl ligand. Kuhn and Mayr have determined the rate constant of the irreversible reaction of secondary amines (piperidine, morpholine) with $[(\eta^3\text{-}PhCHCHCH_2)Pd(PPh_3)_2]^+$ in CH_2Cl_2.[7] Jutand et al. have determined the rate constant of the irreversible reaction of morpholine with $[(\eta^3\text{-}CH_2CHCH_2)Pd(PAr_3)_2]^+$ (Ar = 4-Cl-C_6H_4, 4-Me-C_6H_4) in DMF.[8] The latter reactions were found to be faster than those of the neutral complexes $(\eta^1\text{-}CH_2{=}CHCH_2)PdCl(PAr_3)_2$ generated upon addition of chloride ions to the cationic complexes $[(\eta^3\text{-}CH_2CHCH_2)Pd(PAr_3)_2]^+$.[8,9]

The mechanism of the reaction of (*E*)-PhCH=CHCH(Ph)-OAc (an allylic acetate specifically designed by Trost et al. to test the effect of chiral ligands on the enantioselectivity of Pd-catalyzed nucleophilic allylic substitutions)[10] with Pd^0L_2 (L = PPh_3, L_2 = dppb =1,4-bis(diphenylphosphino)butane) has been fully established in our group,[2e] and the cationic complexes $[(\eta^3\text{-}PhCHCHCHPh)PdL_2]^+$ (L = PPh_3, L_2 = dppb) formed in these reactions have been fully characterized.[2e]

We report herein the mechanism of the reaction of secondary amines (morpholine, piperidine) with cationic complexes $[(\eta^3\text{-}PhCHCHCHPh)PdL_2]^+$ (L = PPh_3, L_2 = dppb). PPh_3 and dppb were selected as representative of monodentate and bidentate ligands, respectively. The kinetics of the successive steps of palladium-catalyzed allylic aminations,[11] i.e., oxidative addition leading to the cationic complex[2e] followed by its nucleophilic attack by the amine reported in the present work, can now be compared with each other to define the rate-determining step of the catalytic cycle.

Results and Discussion

Rate and Mechanism of the Reaction of Amines (Morpholine, Piperidine) with the Cationic Complex $[(\eta^3\text{-}PhCHCHCHPh)Pd(PPh_3)_2]^+BF_4^-$ in DMF. (a) Reaction with Morpholine. The reaction of $Pd^0(PPh_3)_2$ with (*E*)-PhCH=CHCH(Ph)OAc gives the complex $[(\eta^3\text{-}PhC_3H_3Ph)Pd(PPh_3)_2]^+$-$AcO^-$ in a reversible reaction.[2e] Consequently, the latter complex could not be isolated with AcO^- as the counteranion. The reaction with morpholine was thus investigated on the isolated stable complex $[(\eta^3\text{-}PhC_3H_3Ph)Pd(PPh_3)_2]^+BF_4^-$ (**1a**$^+BF_4^-$).[2e] The reaction was followed by UV spectroscopy. As previously reported, the complex **1a**$^+$ exhibits an absorption band at λ_{max} 345 nm in DMF (Figure 1).[2e] It totally disappeared only after addition of 2 equiv of morpholine, attesting to a facile reaction between the nucleophile and **1a**$^+$. The final value of the absorbance was similar, whatever the amount of added morpholine ($n \geq 2$ equiv), evidencing that the overall reaction was irreversible.

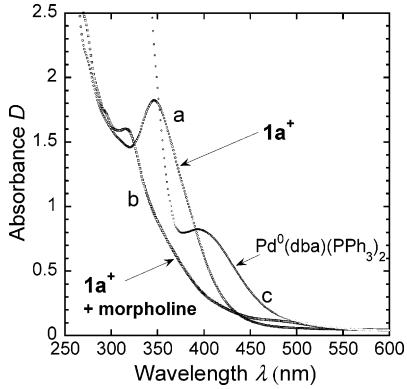

Figure 1. Reaction of $[(\eta^3\text{-}PhCHCHCHPh)Pd(PPh_3)_2]^+BF_4^-$ (**1a**$^+BF_4^-$) with morpholine in DMF at 10 °C, as monitored by UV spectroscopy in a 1 mm cell: (a) **1a**$^+BF_4^-$, C_0 = 1 mM; (b) **1a**$^+BF_4^-$ + morpholine (2 equiv); (c) $Pd^0(dba)(PPh_3)_2$ formed after addition of dba (2 equiv) to (b).

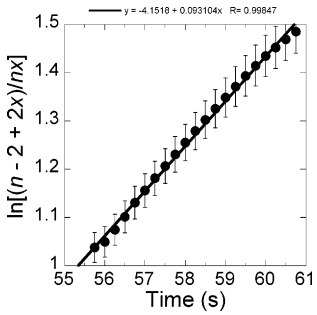

Figure 2. Kinetics of the reaction of morpholine (5.99 mM) with $[(\eta^3\text{-}PhC_3H_3Ph)Pd(PPh_3)_2]^+BF_4^-$ (C_0 = 1 mM) in DMF at 10 °C, as monitored by UV spectroscopy at 345 nm, performed in a 1 mm cell:[14] plot of $\ln[(n - 2 + 2x)/nx]$ versus time (see eq 2).

The absorption band of $Pd^0(dba)(PPh_3)_2$ at λ_{max} 400 nm[2e] appeared after addition of dba (2 equiv). This indicates that the reaction of morpholine with **1a**$^+$ produced the stable Pd^0 complex **2m**,[12] whose reaction with dba generated $Pd^0(dba)$-$(PPh_3)_2$ and the final substitution product **3m** (Scheme 2). The latter was characterized by comparison with an authentic sample synthesized by reacting morpholine with PhCH=CHCH(Ph)-OAc in the presence of $Pd^0(PPh_3)_4$ (10%) in dichloromethane (vide infra).

The UV spectrum in Figure 1 (curve b) recorded after reaction of morpholine with **1a**$^+$, in the absence of dba, exhibited a new absorption band at λ_{max} 315 nm. This band characterized the Pd(0) complex **2m**. Indeed, the UV spectrum of $Pd^0(PPh_3)_4$ (1 mM in DMF) exhibited an absorption band at λ_{max} 323 nm. After addition of an authentic sample of the substitution product **3m** (10 mM), a new band was observed at λ_{max} 317 nm, attesting to a complexation of $Pd^0(PPh_3)_2$ to **3m**, as in the Pd(0) complex **2m**.[8,12] The reaction of morpholine (0.02 mmol) with **1a**$^+BF_4^-$ (0.01 mmol) in acetone-d_6 (0.5 mL) was followed by ^1H and ^{31}P NMR spectroscopy. The substitution product **3m** was detected on the first recorded ^1H spectrum without the signals

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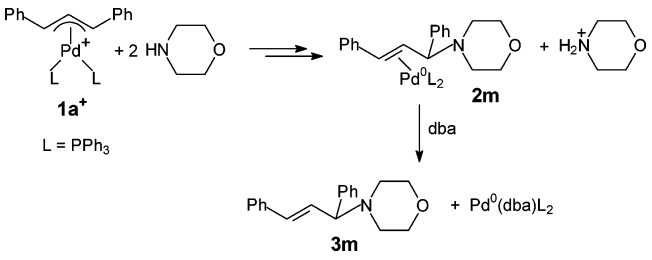
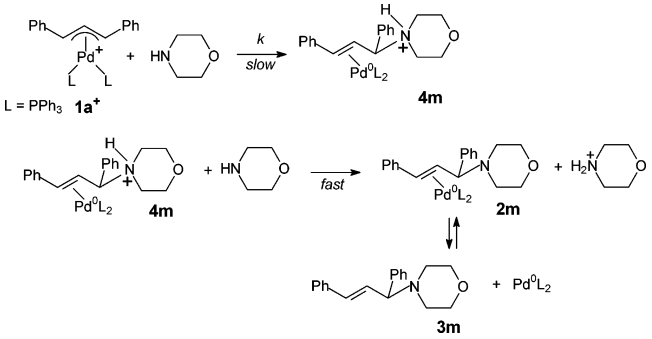
(12) For coordination of Pd^0 to the C=C bond of the final substitution product see ref 8 and: Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed.* **1997**, *36*, 2108−2110.

Scheme 2



Scheme 3



of $\mathbf{1a}^+BF_4^-$,[2e] attesting to a fast reaction. Two broad multiplets centered at 6.70 and 7.01 ppm were assigned to the two vinylic protons of complex **2m**.[13] When the same reaction was performed in CD_2Cl_2, two similar broad multiplets were observed at 6.65 and 6.96 ppm, associated with two broad ^{31}P NMR signals at 30.74 and 28.66 ppm of same magnitude, characteristic of two nonmagnetically equivalent PPh_3 groups. They were assigned to complex **2m**.

Jutand et al.[8] have established that the reaction of morpholine with $[(\eta^3\text{-}CH_2CHCH_2)Pd(PAr_3)_2]^+BF_4^-$ proceeds via two successive irreversible steps. The first one, the nucleophilic attack of the amine at the allyl ligand, is rate-determining. By similarity, the mechanism of the reaction of $\mathbf{1a}^+BF_4^-$ with morpholine is proposed in Scheme 3. Note that the fate of the Pd(0) complex **2m** (equilibrium with **3m**) does not interfere in the kinetics of the overall reaction, which is limited by the rate of the first step (vide infra).

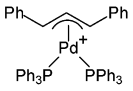
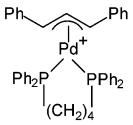
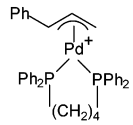
The reaction was too fast to be followed by UV spectroscopy at room temperature. Its kinetics was thus investigated at 10 °C with a low excess of morpholine ($n < 10$ equiv). The decrease of the absorbance D_t of $\mathbf{1a}^+$ at 345 nm was recorded versus time after addition of morpholine. The kinetic law of the mechanism proposed in Scheme 3 is given in eqs 1 and 2, taking into account the variation of the morpholine concentration during the reaction (C_0 = initial concentration of $\mathbf{1a}^+BF_4^-$, n = initial number of equivalents of morpholine, $x = [\mathbf{1a}^+]_t/[\mathbf{1a}^+]_0 = (D_t - D_\infty)/D_0 - D_\infty)$ with D_t being the absorbance of $\mathbf{1a}^+$ at t, D_∞ the final absorbance at infinite time, and D_0 the initial absorbance of $\mathbf{1a}^+$).

$$dx/dt = -kC_0(n - 2 + 2x)x \quad (1)$$

$$\ln[(n - 2 + 2x)/nx] = kC_0(n - 2)t \quad (2)$$

The plot of $\ln[(n - 2 + 2x)/nx]$ against time was linear (Figure 2),[14] confirming a first-order reaction for $\mathbf{1a}^+$. The value of k was determined from the slope of the straight line. Similar values of k were obtained regardless of the concentration of morpholine investigated here ($n = 5.99$, $k = 23.4$ M^{-1} s^{-1}; $n = 7$, $k = 21.8$ M^{-1} s^{-1}; $n = 8.2$, $k = 24.4$ M^{-1} s^{-1}; $n = 9.45$, $k = 25$ M^{-1} s^{-1}), attesting also to a first-order reaction for the morpholine, in agreement with eq 2 and the mechanism proposed in Scheme 3: i.e., nucleophilic attack of the morpholine onto the allyl ligand of $\mathbf{1a}^+$ is the rate-determining step ($k = 23 \pm 1$ M^{-1} s^{-1}; Table 1), followed by the faster deprotonation of **4m** by a second morpholine.

Table 1. Rate or Equilibrium Constants for the Reaction of Morpholine and Piperidine with Cationic $(\eta^3\text{-allyl})PdL_2^+$ Complexes in DMF (see Schemes 3 and 6 for the Definition of k and K)

$(\eta^3\text{-allyl})PdL_2^+$	morpholine	piperidine
 **1a⁺**	$k = 23$ $M^{-1}s^{-1}$ (10 °C)	$k > 23$ $M^{-1}s^{-1}$ (10 °C)
 **1b⁺**	$K = 3\times10^{-6}$ (25 °C)	$K = 2.3\times10^{-4}$ (25 °C)
 **1c⁺**	$K = 1.2\times10^{-3}$ (25 °C)	n.d.

(b) Reaction with Piperidine. The reaction of piperidine with $\mathbf{1a}^+BF_4^-$ gave the allylic piperidine **3p**, as established by ^1H NMR spectroscopy. The reaction was followed by UV spectroscopy at 10 °C, as was done for morpholine. This reaction was considerably faster than the reaction with morpholine, in agreement with their respective pK_A values (11.12 vs 8.21).[15] Though the behavior was similar to the previous case, the rate constant k could not be determined, due to lack of accuracy (Table 1).

Rate and Mechanism of the Reaction of Amines (Morpholine, Piperidine) with the Cationic Complex $[(\eta^3\text{-PhCHCHCHPh})Pd(dppb)]^+BF_4^-$ in DMF. (a) Reaction with Morpholine. As previously reported, the reaction of (*E*)-PhCH=CHCH(Ph)OAc with $Pd^0(dppb)$ gives the complex $[(\eta^3\text{-}PhC_3H_3\text{-}Ph)Pd(dppb)]^+AcO^-$ in a reversible reaction.[2e] The latter complex could not be isolated with AcO^- as the counteranion. The reaction with morpholine was thus investigated on the isolated stable BF_4^- salt, $[(\eta^3\text{-}PhC_3H_3Ph)Pd(dppb)]^+BF_4^-$ ($\mathbf{1b}^+BF_4^-$).[2e] The latter exhibits an absorption band at λ_{max} 352 nm in DMF.[2e] The decrease of the absorbance of $\mathbf{1b}^+BF_4^-$ ($C_0 = 1$ mM) at 352 nm in the presence of morpholine (50 equiv) was recorded with time at 25 °C. The absorbance decreased and stabilized with time but did not reach its expected final value. Furthermore, it decreased again and stabilized after further

(13) (a) The main signal detected in the ^{31}P NMR spectrum was that of triphenylphosphine oxide at 24.94 ppm, together with a minor signal at 35.46 ppm characteristic of $O_2Pd(PPh_3)_2$.[13b] Both were formed by a side reaction of oxygen and the residual water of the solvent with $Pd^0(PPh_3)_2$ released from the Pd(0) complex **2m**. (b) Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829.

(14) The reaction of morpholine (5.99 mM) with $[(\eta^3\text{-}PhC_3H_3Ph)Pd(PPh_3)_2]^+BF_4^-$ was fast. The UV measurements were performed after the cell was shaken by hand just after addition of morpholine to the cationic complex. This requires some time during which the absorbance could not be measured. This is why the first part of the kinetics is missing.

(15) Weast, R. C., Ed. *Handbook of Chemistry and Physics*, 52nd ed.; CRC Press: Cleveland, OH, 1971−1972, p D-177.

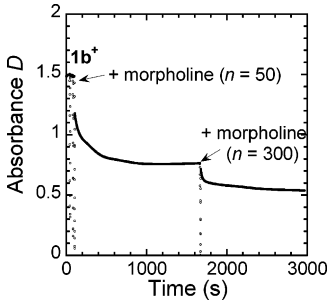


Figure 3. Reaction of morpholine (*n* is the total number of equivalents of added morpholine) with $[(\eta^3\text{-PhCHCHCHPh})Pd(dppb)]^+BF_4^-$ (C_0 = 1 mM) in DMF at 25 °C, as monitored by UV spectroscopy at 352 nm, performed in a 1 mm cell.

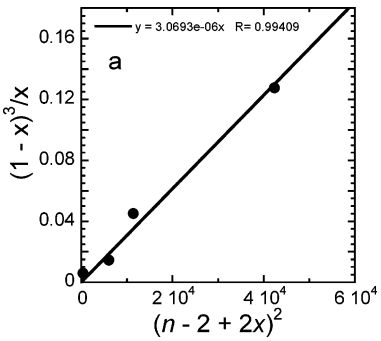


Figure 4. Determination of the *K* value of the equilibrium observed in the reaction of $[(\eta^3\text{-PhC}_3\text{H}_3\text{Ph})Pd(dppb)]^+BF_4^-$ (**1b**$^+BF_4^-$; 1 mM) with morpholine (*n* equiv) in DMF at 25 °C, as monitored by UV spectroscopy at 352 nm, performed in a 1 mm cell. $(1 - x)^3/x = K(n - 2 + 2x)^2$.

addition of morpholine (Figure 3).[16] This establishes that the reaction of morpholine with **1b**$^+$ was reversible.[17]

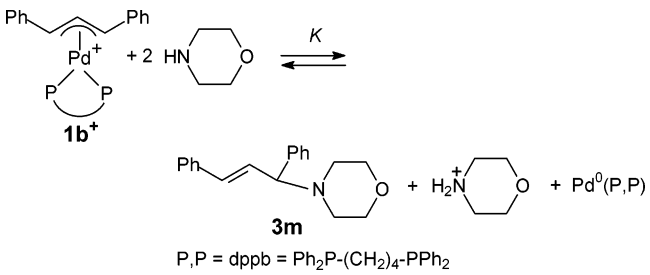
The reaction was also followed by ^{1}H and ^{31}P NMR performed on a solution of **1b**$^+BF_4^-$ in $CDCl_3$ after addition of morpholine (2 equiv). The final substitution product, **3m**, was observed on the ^{1}H NMR spectrum together with protonated morpholine (δ 2.9 (m, 4H), 3.7 (m, 4H), and 4.9 (s, 2H) ppm). The protonated **3m** was not observed. The ^{31}P NMR spectrum exhibited the singlet of unreacted **1b**$^+$ at 22.89 ppm and a singlet at 21.28 ppm but did not exhibit any doublets which would characterize a complex involving a Pd^0(dppb) moiety ligated to the C=C bond of the final compound **3m** or an intermediate product. This confirms that **1b**$^+$ and morpholine remained at equilibrium with the final product **3m**, the protonated morpholine and Pd^0(dppb) (21.28 ppm) (Scheme 4).

The equilibrium constant $K = (1 - x)^3/[x(n - 2 + 2x)^2]_{equil}$ ($x = [\mathbf{1a}^+]_{equil}/[\mathbf{1a}^+]_0 = (D_{equil} - D_\infty)/D_0 - D_\infty$), with D_{equil} being the absorbance of **1b**$^+$ in the presence of *n* equiv of morpholine when the equilibrium was reached, D_∞ the final absorbance when the reaction was made fully irreversible, and D_0 the initial absorbance of **1b**$^+$) was determined by UV spectroscopy. The plot of $(1 - x)^3/x$ versus $(n - 2 + 2x)^2$ was linear, so that the value of *K* was determined from the slope of the straight line (Figure 4, Table 1).

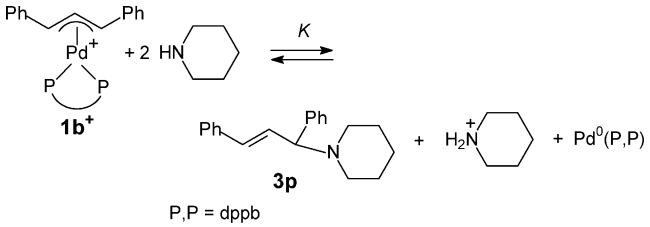
(16) After a while, the solution turned pink and an absorption band at λ_{max} 520 nm was observed, attesting to the formation of degradation products, e.g. Pd^I clusters, as was proposed by: Tromp, M., Sietsma, J. R. A.; van Bokhoven, J. A, van Strijdonck, G. P. F.; van Haaren, R. J.; van der Eerden, A. M. J.; van Leeuwen, P. W. N. M.; Koningsberg, D. C. *Chem. Commun.* **2002**, 128−129.

(17) For the reversibility of nucleophilic attack of cationic (η^3-allyl)-palladium(II) complexes by secondary amines, see ref 1w.

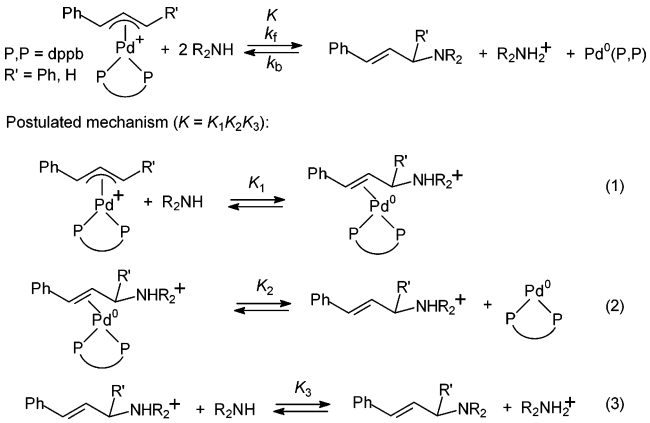
Scheme 4



Scheme 5



Scheme 6

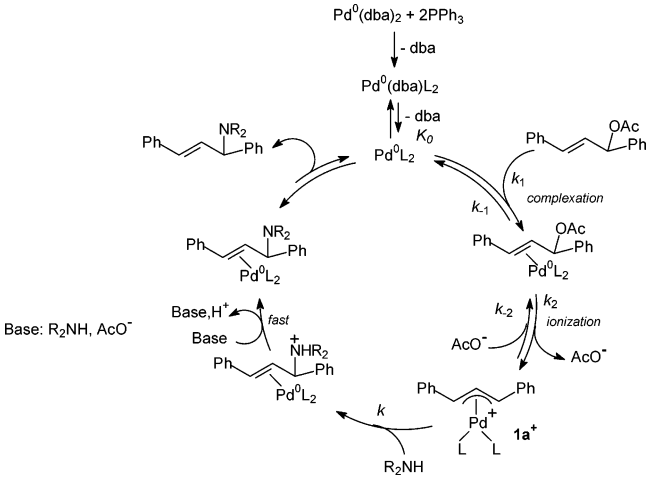


(b) Reaction with Piperidine. The reaction of piperidine with **1b**$^+BF_4^-$ was followed by UV spectroscopy and ^{1}H and ^{31}P NMR, as for morpholine. The reaction was also reversible (Scheme 5). The equilibrium constant *K* was determined by UV spectroscopy (Table 1; see also Figure S1 in the Supporting Information).

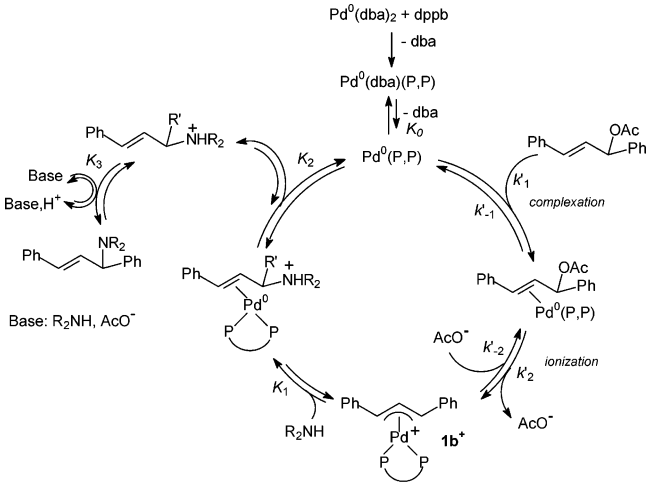
Comparative Reactivities of Morpholine and Piperidine with Cationic Complexes $[(\eta^3\text{-allyl})PdL_2]^+$ and Relevance to the Mechanism of Pd-Catalyzed Allylic Aminations (Monophosphine versus Bisphosphine). The reaction of morpholine and piperidine with complex **1a**$^+$, i.e., when the Pd^{II} was ligated by 2 PPh_3, was irreversible and piperidine was found to be more reactive than morpholine (see *k* in Table 1). The same reactions with **1b**$^+$, i.e., when the Pd^{II} was ligated by the bidentate dppb ligand, were reversible, and the equilibrium lies more toward the final products when using piperidine rather than morpholine (see *K* in Table 1). These results are in agreement with the higher basicity and thus higher reactivity of piperidine.[15]

The fact that the reaction was irreversible when using a monodentate phosphine and reversible when using a bidentate bisphosphine seems to be a general feature. Indeed, as previously reported the reaction was found to be irreversible when reacting morpholine with $[(\eta^3\text{-}CH_2CHCH_2)Pd(PAr_3)_2]^+$ (Ar = 4-Cl-C_6H_4, 4-Me-C_6H_4)[8] or with $[(\eta^3\text{-PhCHCHCH}_2)Pd(PPh_3)_2]^+$.[7] However, the reaction of morpholine with $[(\eta^3\text{-PhCHCHCH}_2)$-Pd(dppb)]$^+$ (**1c**$^+$) investigated in the present work was found

Scheme 7. Mechanism of the Pd-Catalyzed Allylic Amination When L Is a Monophosphine



Scheme 8. Mechanism of the Pd-Catalyzed Allylic Amination When P,P Is the Bisphosphine dppb



to be reversible (Scheme 6 and Table 1; see also Figure S2 in the Supporting information). This suggests that the nucleophilic attack of the amine at the allyl ligand of cationic complexes ligated by a P,P ligand is reversible (eq 1 in Scheme 6). The reverse reaction is an oxidative addition (viz. an activation of a C−N bond), which is indeed expected to be faster with Pd^0(dppb) than with $Pd^0(PPh_3)_2$ because (i) Pd^0(dppb) is intrinsically more nucleophilic and consequently more reactive than $Pd^0(PPh_3)_2$ and (ii) the bite angle of dppb is smaller than the P−Pd−P angle for PPh_3, favoring of the oxidative addition.

Relevance to the Catalytic Cycle of Allylic Aminations (Monophosphine versus Bisphosphine). The present work on the mechanism of nucleophilic attack of secondary amines on $[(\eta^3\text{-}PhC_3H_3Ph)PdL_2]^+$ complexes can be connected to our previous work on the mechanism of formation of such complexes by reacting PhCH═CHCH(OAc)Ph with the related Pd^0L_2 complexes.[2e]

The mechanism of the Pd-catalyzed allylic amination when the palladium is ligated by two monophosphine ligands is presented in Scheme 7. We must now take into account the fact that acetate ions are released in catalytic reactions and can play the role of a base for the deprotonation of the ammonium salt in $(\eta^2\text{-}PhCH{=}CHCH(NHR_2^+)Ph)Pd^0(PPh_3)_2$ if the secondary amine is not used in excess.

The rate of the reaction of morpholine or piperidine with **1a**$^+$ investigated in this work (rate constant k) can be compared to the rate of formation of **1a**$^+$AcO$^-$ in the oxidative addition of (*E*)-PhCH═CHCH(Ph)OAc to $Pd^0(PPh_3)_2$ generated from $Pd^0(dba)_2 + 2PPh_3$ in DMF (Scheme 7).[2e] The complexation step performed from $Pd^0(dba)(PPh_3)_2$ was found to be irreversible as soon as [PhCH═CHCH(Ph)OAc] > 30 mM (k_{obs} > 0.135 s^{-1}).[2e] The slowest step of the overall reaction was the ionization of the intermediate Pd^0 complex $(\eta^2\text{-}PhCH{=}CHCH(Ph)OAc)Pd^0(PPh_3)_2$ to **1a**$^+$AcO$^-$ (Scheme 7). The latter reaction was reversible with $k_2 = 5 \times 10^{-3}$ s^{-1} and $k_{-2} \approx 60$ M^{-1} s^{-1} in DMF at 25 °C. In a catalytic reaction, the secondary amine will therefore be in competition with the acetate ions in their reaction with the cationic complex **1a**$^+$ (Scheme 7). If $k[R_2NH] > k_{-2}[AcO^-]$, the overall fast irreversible nucleophilic attack of the amine in the catalytic reaction will be limited by the ionization step (rate constant k_2), which will be the rate-limiting step of the catalytic cycle. Considering the attack of the morpholine with $k = 23$ M^{-1} s^{-1} at 10 °C (Table 1), k can be estimated to be ca. 90 M^{-1} s^{-1} at 25 °C, assuming an average activation enthalpy. In a catalytic reaction involving 2 equiv of morpholine per PhCH═CHCH(Ph)OAc, one has k[morpholine] > k_{-2}[AcO$^-$] up to a 75% conversion. The nucleophilic attack of morpholine on **1a**$^+$ will be faster than the attack of AcO$^-$ and thus will be limited by the ionization step (rate constant k_2). This is in contradiction with the postulated mechanism of the palladium-catalyzed nucleophilic substitution, which supposes that the nucleophilic attack on cationic (η^3-allyl)palladium(II) complexes is slower than the fast overall oxidative addition.[1]

The mechanism of the Pd-catalyzed allylic amination when the palladium is ligated by a bisphosphine ligand is presented in Scheme 8. It takes into account the role of acetate ions released in the course of the catalytic reaction, which can compete with the amine in the reversible deprotonation of the free ammonium $PhCH{=}CHCH(NHR_2^+)Ph$.

The oxidative addition was found to be reversible when the catalytic precursor is $Pd^0(dba)_2$ associated with dppb (1 equiv) (Scheme 8).[2e] Consequently, all steps of the catalytic cycle are reversible (Scheme 8). The overall equilibrium which releases the final substitution product $PhCH{=}CHCH(NHR_2)Ph$ after the ionization step might be made irreversible under the conditions of catalytic reactions upon depleting the free ammonium $PhCH{=}CHCH(NHR_2^+)Ph$ by using a base which is stronger than acetate, piperidine, or morpholine but which is not nucleophilic and cannot attack the allyl ligand or the Pd^{II} center.[18]

The complexation step performed from Pd^0(dba)(dppb) was found to be irreversible as soon as [PhCH═CHCH(Ph)OAc] > 10 mM ($k_{obs} > 5.3 \times 10^{-3}$ s^{-1}).[2e] The reversible ionization step lies more toward the cationic complex **1b**$^+$ in comparison to the same step involving PPh_3 with $k'_2 = 3 \times 10^{-4}$ s^{-1} and $k'_{-2} < 3 \times 10^{-7}$ M^{-1} s^{-1} in DMF at 25 °C.[2e] However, the slowest step of the overall reaction of Pd^0(dba)(dppb) and PhCH═CHCH(Ph)OAc is still the ionization of the intermediate $(\eta^2\text{-}PhCH{=}CHCH(Ph)OAc)Pd^0$(dppb) to **1b**$^+AcO^-$ (Scheme 8).[2e]

Considering the reversible nucleophilic attack of morpholine onto complex **1b**$^+$ in Scheme 6, with the equilibrium constant $K = 3 \times 10^{-6}$ (Table 1), one can calculate that 18 000 equiv of morpholine would be required to make the equilibrium in Scheme 6 (R = Ph) fully shifted toward its right-hand side. Such reaction would, however, be too fast to allow the calculation of the forward rate constant (k_f) of the overall

(18) It is also expected that any other ligand of the Pd^0(dppb) moiety, as dba in catalytic reactions, will interfere in the equilibrium which releases the Pd^0(dppb) complex by formation of Pd^0(dba)(dppb) (Scheme 8).

equilibrium. The forward rate constant k_f was thus estimated from the initial slope of the curve obtained in Figure 3, after addition of morpholine to complex **1b**$^+$ (at $t = 1670$ s in Figure 3). This gives: $k_f \approx 0.1$ M^{-2} s^{-1} (DMF, 25 °C). In catalytic reactions involving 2 equiv of morpholine/equiv of PhCH═CHCH(Ph)OAc (initial concentration C_0), one has k_f[morpholine]$^2 \gg k'_{-2}$[AcO$^-$], as soon as $C_0 > 10^{-4}$ M. Consequently, the nucleophilic attack of morpholine on **1b**$^+$ is always faster than the attack of AcO$^-$ in the usual catalytic reactions and thus may be limited by the slow ionization step. This effect will be amplified for the more reactive piperidine.

Conclusion

The reaction of amines (piperidine, morpholine) with cationic complexes [(η^3-PhCHCHCHPh)PdL$_2$]$^+$ (L = PPh$_3$, L$_2$ = dppb) has been investigated in DMF. It proceeds via the attack at the allyl ligand. This reaction is irreversible when L = PPh$_3$, whereas it is reversible when considering the bidentate ligand dppb. In both cases, piperidine is more reactive than morpholine. These results can be connected to our previous work on the mechanism and kinetics of the reaction of (*E*)-PhCH═CHCH(Ph)OAc with Pd^{0}L$_2$ (L = PPh$_3$, L$_2$ = dppb),[2e] which gives the cationic complexes [(η^3-PhCHCHCHPh)PdL$_2$]$^+$. Entire catalytic cycles are now proposed for the Pd-catalyzed allylic amination of (*E*)-PhCH═CHCH(Ph)OAc by piperidine or morpholine, where the mechanisms of all steps have been established, including characterization of all active intermediate Pd(0) or Pd(II) complexes and their reactivities as well (Schemes 7 and 8). It appears that the nucleophilic attack of piperidine and morpholine on [(η^3-PhCHCHCHPh)PdL$_2$]$^+$ is in competition with the nucleophilic attack of acetate ions generated in the ionization step. The nucleophilic attack of the amine might thus be limited by the slow ionization step in which the cationic complex [(η^3-PhCHCHCHPh)PdL$_2$]$^+$ is formed, the ionization being turnover limiting for the catalytic cycle in the usual catalytic reactions.

Experimental Section

General Considerations. ^{31}P NMR spectra were recorded in acetone-d_6 on a Bruker spectrometer (101 MHz) with H_3PO_4 as an external reference. ^{1}H NMR spectra were recorded in acetone-d_6 of $CDCl_3$ on a Bruker spectrometer (250 MHz). UV spectra were recorded on an mc^2 Safas Monaco spectrometer. All experiments were performed under an argon atmosphere.

Chemicals. DMF was distilled from calcium hydride under vacuum and kept under argon. dba, morpholine, and piperidine were obtained from commercial sources. [(η^3-PhCHCHCHPh)Pd(PPh$_3$)$_2$]$^+$-BF$_4^-$ and [(η^3-PhCHCHCHPh)Pd(dppb)]$^+$BF$_4^-$ were synthesized as reported in our previous work.[2e]

Synthesis of [(η^3-PhCHCHCH$_2$)Pd(dppb)]$^+$BF$_4^-$. dppb (0.166 g, 0.4 mmol) in 6 mL of acetone was added to a solution of [Pd(η^3-Ph−CH−CH−CH$_2$)(μ-Cl)]$_2$[1a] (0.102 g, 0.2 mmol) in 4 mL of acetone. 4 mL of water was then added, followed by $NaBF_4$ (0.322 g, 3.0 mmol) in 8 mM of water. A yellow solid was formed after 25 min. After filtration, the yellow solid was dissolved in dichloromethane and crystallized from petroleum ether. A 127 mg amount of [(η^3-PhCHCHCH$_2$)Pd(dppb)]$^+$BF$_4^-$ was collected (43% yield). ^{1}H NMR (250 MHz, acetone-d_6, TMS): δ 1.76 (m, 4H), 2.6 (m, 4H), 3.15 (dd, 1H, $J_{HH} = 12$ Hz, $J_{PH} = 5$ Hz), 3.90 (dd, 1H, $J_{HH} = 7$ Hz, $J_{PH} = 7$ Hz), 5.19 (dd, 1H, $J_{HH} = 12$ Hz, $J_{PH} = 5$ Hz), 6.45 (sext, 1H, $J_{HH} = 12$ Hz, $J_{HH} = 12$ Hz, $J_{HH} = 7$ Hz), 6.84−7.71 (m, 25H). ^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ 1.7−2.9 (m, 8H), 3.41 (dd, 1H, $J_{HH} = 12$ Hz, $J_{PH} = 5$ Hz), 3.68 (dd, 1H, $J_{HH} = 7$ Hz, $J_{PH} = 7$ Hz), 5.16 (dd, 1H, $J_{HH} = 12$ Hz, $J_{PH} = 5$ Hz), 6.08 (sext, 1H, $J_{HH} = 12$ Hz, $J_{HH} = 12$ Hz, $J_{HH} = 7$ Hz), 6.8−7.5 (m, 25H); ^{31}P NMR (101.6 MHz, acetone-d_6, H_3PO_4): δ 19.26 (d, 1P, $J_{PP} = 54$ Hz), 25.50 (d, 1P, $J_{PP} = 54$ Hz). ^{31}P NMR (101.6 MHz, $CDCl_3$, H_3PO_4): δ 17.12 (d, 1P, $J_{PP} = 54$ Hz), 23.07 (d, 1P, $J_{PP} = 54$ Hz). FAB-MS (MB 001): *m/z* 649 [M]$^+$, 532 [M − PhC$_3$H$_4$]$^+$.

General Procedure for the Reaction of 1a$^+$BF$_4^-$, 1b$^+$BF$_4^-$, and 1c$^+$BF$_4^-$ with Morpholine or Piperidine, As Monitored by UV Spectroscopy. A 300 μL aliquot was transferred under argon to a UV cell thermostated at 10 °C (1 mm length) from a mother solution of 5 mL of DMF containing 4.5 mg (5 μmol, 1 mM) of **1a**$^+$BF$_4^-$. UV measurements were performed (Figure 1a). These were followed by addition of 2 equiv of morpholine from a mother solution. UV measurements were again performed (Figure 1b). Two equivalents of dba (10 μL from a mother solution containing 28 mg (0.12 mmol) of dba in 2 mL of DMF) was then added, and the UV measurements were performed (Figure 1c). In other experiments, the kinetics of the reaction was followed by recording the absorbance of **1a**$^+$BF$_4^-$ at 345 nm with time after addition of a known amount of morpholine (or piperidine) immediately after shaking the cell by hand (Figure 2).

Similar experiments were performed for the reaction of **1b**$^+$BF$_4^-$ (mother solution of 5 mL of DMF containing 4.1 mg (5 μmol, 1 mM) of **1b**$^+$BF$_4^-$) with morpholine and piperidine. The absorbance of **1b**$^+$BF$_4^-$ at 352 nm was recorded with time after successive addition of known amounts of morpholine (Figure 3) or piperidine.

Similarly, UV spectroscopy was performed at 25 °C on 300 μL of a mother solution of **1c**$^+$BF$_4^-$ (7.2 mg, 1 mmol in 10 mL of DMF) in a 1 mm cell. The UV was performed after addition of various amounts of morpholine from a mother solution (0.25 mL of morpholine in 5 mL of DMF).

Procedure for the Reaction of 1a$^+$BF$_4^-$ with Morpholine or Piperidine, As Monitored by ^{1}H and ^{31}P NMR Experiments. A 3.8 mg amount (5 μmol) of **1a**$^+$BF$_4^-$ was introduced into an NMR tube containing 0.5 μL of acetone-d_6, followed by 1 μL (10 μmol) of morpholine. The solution turned orange without formation of palladium black. The ^{1}H and ^{31}P NMR signals[2e] of **1a**$^+$ were not detected on the first recorded NMR spectra, attesting to a fast reaction. The substitution product **3m** was formed, exhibiting the same signals as those of an authentic sample. ^{1}H NMR (250 MHz, acetone-d_6, TMS): δ 2.22 (m, 2H), 2.36 (m, 2H), 3.48 (t, $J = 5$ Hz, 4H), 3.72 (d, $J = 9$ Hz, 1H), 6.24 (dd, $J = 16$ Hz, $J = 9$ Hz, 1H), 6.53 (d, $J = 16$ Hz, 1H), 7.01−7.30 (m, 10 H). MS (CI + NH$_3$): *m/z* 280 [M + H]$^+$, 193 [M − C$_4$H$_8$NO] (100%).

In another experiment, 3.8 mg (5 μmol) of **1a**$^+$BF$_4^-$ was introduced into an NMR tube containing 0.5 μL of acetone-d_6, followed by 1 μL (10 μmol) of piperidine. The coupling product **3p** was formed, exhibiting the same signals as those of an authentic sample. ^{1}H NMR (250 MHz, acetone-d_6, TMS): δ 1.35 (m, 6H), 2.20 (m, 2H), 2.34 (m, 2H), 3.73 (d, $J = 9$ Hz, 1H), 6.25 (dd, $J = 16$ Hz, $J = 9$ Hz, 1H), 6.48 (d, $J = 16$ Hz, 1H), 7.01−7.40 (m, 10 H). MS (CI + CH$_4$): *m/z* 278 [M + H]$^+$, 193 [M − C$_5$H$_{10}$N] (100%).

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Supporting Information Available: Figures giving determinations of equilibrium constants for the reactions of piperidine with **1b**$^+$BF$_4^-$ and morpholine with **1c**$^+$BF$_4^-$. This material is available free of charge via the Internet at http://pubs.acs.org.

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