

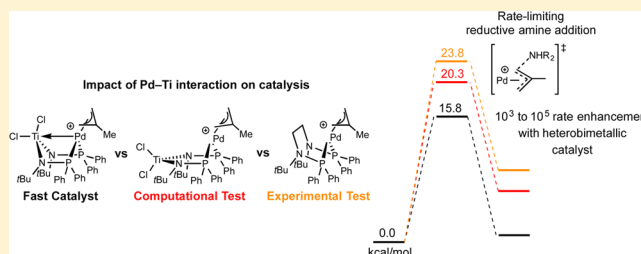
Origin of Fast Catalysis in Allylic Amination Reactions Catalyzed by Pd–Ti Heterobimetallic Complexes

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S Supporting Information

ABSTRACT: Experiments and density functional calculations were used to quantify the impact of the Pd–Ti interaction in the cationic heterobimetallic $\text{Cl}_2\text{Ti}(\text{N}^t\text{BuPPh}_2)_2\text{Pd}(\eta^3\text{-methallyl})$ catalyst **1** used for allylic aminations. The catalytic significance of the Pd–Ti interaction was evaluated computationally by examining the catalytic cycle for catalyst **1** with a conformation where the Pd–Ti interaction is intact versus one where the Pd–Ti interaction is severed. Studies were also performed on the relative reactivity of the cationic monometallic $(\text{CH}_2)_2(\text{N}^t\text{BuPPh}_2)_2\text{Pd}(\eta^3\text{-methallyl})$ catalyst **2** where the Ti from catalyst **1** was replaced by an ethylene group. These computational and experimental studies revealed that the Pd–Ti interaction lowers the activation barrier for turnover-limiting amine reductive addition and accelerates catalysis up to 10^5 . The Pd–Ti distance in **1** is the result of the N^tBu groups enforcing a boat conformation that brings the two metals into close proximity, especially in the transition state. The turnover frequency of classic Pd π allyl complexes was compared to that of **1** to determine the impact of P–Pd–P coordination angle and ligand electronic properties on catalysis. These experiments identified that cationic $(\text{PPh}_3)_2\text{Pd}(\eta^3\text{-CH}_2\text{C}(\text{CH}_3)\text{CH}_2)$ catalyst **3** performs similarly to **1** for allylic aminations with diethylamine. However, computations and experiment reveal that the apparent similarity in reactivity is due to very fast reaction kinetics. The higher reactivity of **1** versus **3** was confirmed in the reaction of methallyl chloride and 2,2,6,6-tetramethylpiperidine (TMP). Overall, experiments and calculations demonstrate that the Pd–Ti interaction induces and is responsible for significantly lower barriers and faster catalysis for allylic aminations.



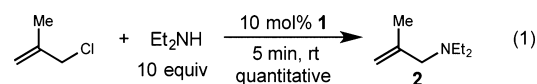
INTRODUCTION

Heterobimetallic transition-metal complexes represent an underutilized and potentially highly useful class of catalysts in organic synthesis.¹ Heterobimetallic complexes offer the ability to enhance the reactivity of a metal center through a direct transition-metal–transition-metal interaction.² Our experimental and computational groups are particularly interested in catalysts that have a dative metal–metal interaction between late and early transition-metal centers.³ The combination of electronically dissimilar metals with a dative interaction in a single catalyst has the potential to significantly alter the electron density and Lewis acidity at the reactive metal center and facilitate oxidation state changes.⁴

Over the past several years there has been a resurgence in the design and synthesis of transition-metal heterobimetallic complexes with dative metal–metal interactions.³ Despite these significant synthetic efforts, however, transition-metal heterobimetallic catalysts are not widely used in organic synthesis, and a quantitative understanding of how dative transition-metal–transition-metal interactions in heterobimetallic complexes impact catalysis is lacking.⁵ A concrete understanding of how heterobimetallic metal–metal interactions accelerate catalysis will enable the development of new heterobimetallic catalysts and new uses in synthetic organic reactions. This stimulated our groups to use computation and experiment to identify, quantify,

and test the enhanced catalysis for Pd–Ti heterobimetallic complexes in allylic amination reactions.⁶

Nagashima recently reported that cationic heterobimetallic $\text{Cl}_2\text{Ti}(\text{N}^t\text{BuPPh}_2)_2\text{Pd}(\eta^3\text{-CH}_2\text{C}(\text{CH}_3)\text{CH}_2)$ complex **1** is capable of catalyzing the allylic amination between methallyl chloride and diethylamine to generate **2** (eq 1).⁷ To illustrate

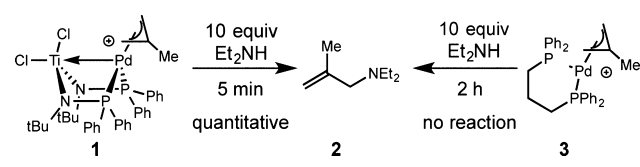


the difference in reactivity between heterobimetallic catalyst **1** and a monometallic Pd catalyst, Nagashima also reported the stoichiometric reaction of Et_2NH with complex **1** and with the cationic bis(diphenylphosphino)propane $\text{Pd}(\text{dppp})$ complex **3** (Scheme 1). For complex **1**, complete Et_2NH addition to generate allyl amine **2** was accomplished in <5 min at room temperature. In contrast, complex **3** did not undergo Et_2NH addition after several hours.

Based on the results in Scheme 1, Nagashima suggested that the Pd–Ti dative interaction in complex **1** provides enhanced reactivity during allylic amination catalysis. However, the different ligand composition, geometry, and electronics of

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Scheme 1. Stoichiometric Studies Previously Reported for Reductive Amine Addition⁷

complexes **1** and **3** may also explain their divergent reactivity. For example, Pd–Ti complex **1** contains a bidentate phosphinoamide ligand and has a different P–Pd–P coordination angle compared to complex **3**, both of which can significantly impact catalysis.⁸ This makes comparison between complexes **1** and **3** neither directly nor quantitatively a good measure of the impact of the Pd–Ti interaction on catalytic reactivity. It therefore remains unclear whether classic ligand effects, the Pd–Ti interaction, or a combination of both effects is responsible for efficient allylic amination catalysis with heterobimetallic complex **1**.

We now report experiments and density functional calculations designed to identify the origin of fast catalysis by complex **1** and quantify the impact of the Pd–Ti interaction versus P–Pd–P coordination angle and ligand composition. The major results presented are: (1) The direct dative Pd–Ti interaction in catalyst **1** is critical for fast Pd^{II} to Pd⁰ reduction upon amine addition to a Pd(methylallyl) intermediate. This was determined by computational analysis of the complete allylic amination catalytic cycle using catalyst **1** in a conformation where the Pd–Ti interaction is intact compared to a conformation with the interaction severed. This result was confirmed by synthesizing and experimentally and computationally evaluating the reactivity of a monometallic phosphinoamide Pd complex where the TiCl₂ in catalyst **1** was replaced by an ethylene group. (2) Monometallic complexes can still effectively catalyze allylic aminations with secondary amines; experimental evaluations of monometallic Pd catalysts revealed that cationic (PPh₃)₂Pd(η³-CH₂C(CH₃)CH₂) complex catalyzes allylic amination with a turnover frequency (TOF) similar to that of catalyst **1**. However, calculations and experiment revealed that the heterobimetallic Pd–Ti catalyst induces a lower activation barrier than all monometallic Pd catalysts. The apparent similar reactivity between the heterobimetallic and monometallic Pd catalysts is due to an inability to measure very fast reaction kinetics. (3) Catalyst **1** is shown to have a much higher reactivity than monometallic Pd catalysts for sterically congested amine substrates, such as 2,2,6,6-tetramethylpiperidine (TMP).

RESULTS AND DISCUSSION

Computational Assessment of Heterobimetallic Pd–Ti Complex **1** and Mechanism for Allylic Amination.

We first used density functional calculations to confirm the mechanism of allylic amination with heterobimetallic complex **1** and to quantify the impact of the Pd–Ti interaction on each step of the catalytic reaction. All SMD solvated free energies (ΔG) refer to M06/6-311+G(2d,p)[LANL2TZ(f)]//M06/6-31G(d,p)[LANL2DZ]. Catalytic and stoichiometric reactions between palladium η³-allyl complexes have been studied extensively by experiment and computation.^{9,10} Similar to previous studies, we found after extensive exploration of possible mechanisms that the lowest-energy mechanism catalyzed by the heterobimetallic catalyst **1** involves outer-sphere amine addition followed by ligand exchange (**4** to **5**) and then inner-sphere

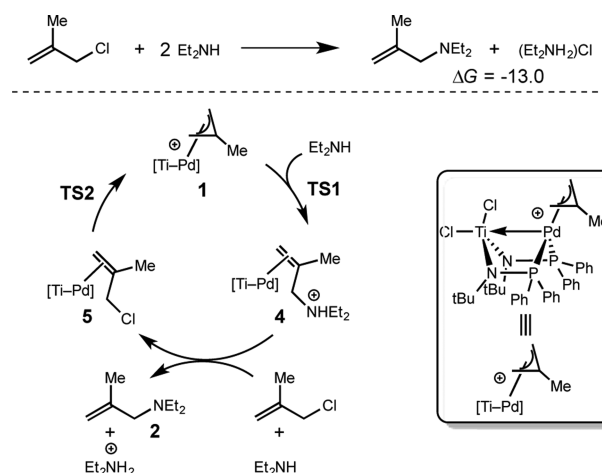


Figure 1. Calculated mechanism for allylic amination catalyzed by **1** (kcal/mol).

Pd⁰ to Pd^{II} oxidation by substitution at the allyl chloride to regenerate **1** (Figure 1). For catalyst **1**, we confirmed that inner-sphere amine-allyl reductive elimination, C–Cl bond oxidative insertion, and Lewis acid S_N2 reaction pathways were all higher in energy than the mechanism shown in Figure 1 (energies listed in Supporting Information).

For the mechanism in Figure 1, catalysis begins with transition state **TS1** where Et₂NH nucleophilically adds to one of the terminal η³-allyl carbons and results in Pd^{II} to Pd⁰ reduction to give the Pd(η²-methylallyl ammonium) complex **4**. This reaction step requires $\Delta G^\ddagger = 15.8$ kcal/mol and is endergonic by 1.6 kcal/mol, relative to catalyst **1**, Et₂NH, and methylallyl chloride (Figure 2a). We also examined the possibility that multiple Et₂NH molecules create a hydrogen-bond network in **TS1**. While there is a few kcal/mol lower ΔH^\ddagger due to enhanced nucleophilicity for (Et₂NH)₂ compared to Et₂NH, entropy effects result in a higher ΔG^\ddagger for addition. In **TS1**, the Pd–Ti interaction increases, as indicated by the Pd–Ti distance that shortens to 2.77 Å (Figure 2b) compared to the 2.88 Å distance in the ground state of **1**. Additionally, the P–Pd–P coordination angle increases slightly to 106° compared to the 104° angle in **1**. Interpretation of the Pd–Ti distance decrease suggests that there is indeed a direct through-space stabilization of the increasing electron density at the Pd metal center upon Et₂NH reductive addition.

After dissociation of the allyl ammonium intermediate and coordination of the allyl chloride (**4** to **5**, Figure 1) that is approximately thermoneutral, the π-allyl catalyst **1** is regenerated when the Pd⁰ metal center (**5**) nucleophilically forms a Pd–C bond to the backside of the C–Cl bond with simultaneous chloride ejection in an intramolecular substitution reaction (**TS2**, Figure 2b). One concern from the viewpoint of catalyst performance and future catalyst design is that formation of a Pd–Ti interaction could overstabilize the Pd⁰ intermediate and ultimately be deleterious to catalysis by raising the barrier for oxidative addition (see later discussion for comparison to monometallic catalysts), the effect is not sufficient to cause Pd⁰ to Pd^{II} oxidation to become rate limiting. The Pd⁰ to Pd^{II} oxidative transition state (**TS2**, Figure 2a) with complex **1** requires $\Delta G^\ddagger = 7.8$ kcal/mol and is 8.0 kcal/mol lower than **TS1**. We worried that the free-energy surface may overestimate the entropy penalty for **TS1** compared to **TS2**. However, using entropy values scaled by 50% still shows that the ΔG^\ddagger for **TS1**

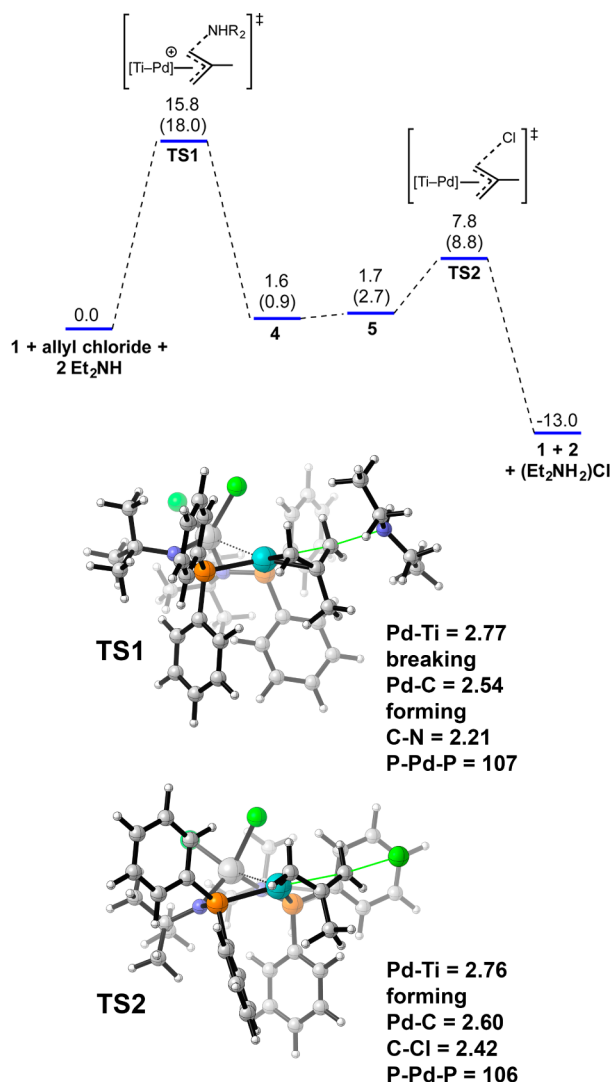


Figure 2. (Top) M06 free energy landscape for Et₂NH reductive addition and methallyl chloride-induced Pd⁰ to Pd^{II} oxidation. ωB97X-D free energy values given in parentheses. Free energies in kcal/mol. (Bottom) Transition-state structures. Bond lengths reported in Å.

is ~ 4 kcal/mol higher in energy than the ΔG^\ddagger for TS2. The transition-state geometry of TS2 is similar to TS1 (Figure 2b). The lower barrier for TS2 compared to TS1 combined with endergonic intermediates 4 and 5 results in the rate of catalytic turnover being controlled by the energy of the Et₂NH reductive addition step. This indicates that catalytic efficiency is directly linked to lowering the reduction potential of Pd^{II} by stabilizing the resulting Pd⁰ species.

We also examined the possibility that **1** transforms prior to catalysis. Figure 3 shows some of the several possible transformations that were examined. For example, dissociation of one phosphine from Pd and coordination to Ti could generate

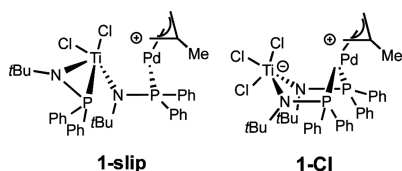


Figure 3. Possible alternative species involved in catalysis.

a more electron-deficient and more reactive unsaturated Pd intermediate, leading to faster catalysis independent of the Pd–Ti interaction (**1-slip**). While **1-slip** is only endergonic by 11.5 kcal/mol, the ΔG^\ddagger for amine addition referenced to **1** is 25.5 kcal/mol, which is significantly higher in free energy than TS1. Chloride and Et₂NH coordinated to Pd with a phosphine ligand slipped to Ti also have ΔG^\ddagger values for amine addition larger than TS1. The large buildup of chloride concentration in the reaction prompted us to examine the possibility of chloride coordination to both Ti and Pd metal centers. Addition of chloride to the Ti metal center and simultaneous coordination expansion to give **1-Cl** is exergonic by only 0.8 kcal/mol relative to complex **1** and free chloride.¹¹ Chloride coordination to Ti results in disintegration of the Pd–Ti interaction and the ΔG^\ddagger for amine addition is 22.7 kcal/mol and is not viable. This indicates that at high chloride concentration catalysis operates by chloride dissociation and then the catalytic cycle shown in Figure 1 rather than a new reaction pathway. We further examined the possibility that Et₂NH exchanges a Ti–Cl ligand to form cationic (Cl)(Et₂N)Ti(N^tBuPPh₂)₂Pd(η^3 -CH₂C(CH₃)CH₂). Similar to **1-Cl**, the Ti amido complex destroys the Pd–Ti interaction and results in a larger activation barrier (see Supporting Information).

To quantify the effect of the direct Pd–Ti interaction on catalysis, we calculated the catalytic cycle free energies using the conformation **1 (flat)** and compared them to those of **1 (boat)** (Figures 4 and 5).¹² Figure 4 shows that when the Pd–Ti

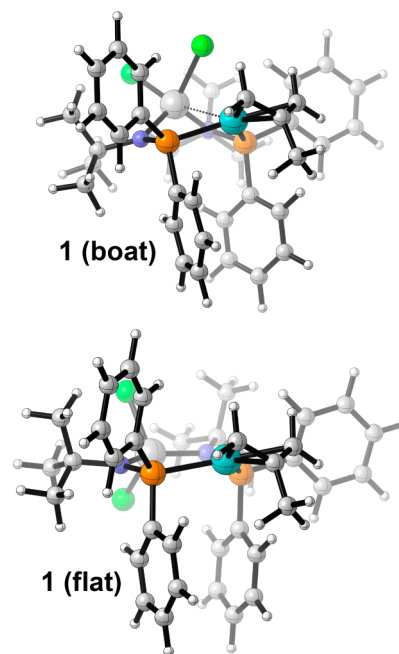


Figure 4. Boat and flat conformations of catalyst **1**.

interaction is severed the ΔG^\ddagger for Et₂NH reductive addition to the Pd(η^3 -CH₂C(CH₃)CH₂) fragment is 20.3 kcal/mol and for Pd oxidation/methallyl chloride substitution is 10.2 kcal/mol. These barriers for TS1 (**flat**) and TS2 (**flat**) are 4.5 and 2.4 kcal/mol larger than the corresponding transition states with **1 (boat)**. The $\Delta\Delta G^\ddagger$ of 4.5 kcal/mol for turnover-limiting Et₂NH reductive addition suggests that the Pd–Ti interaction is responsible for $\sim 10^3$ rate enhancement. The lower barrier for TS1 (**boat**) compared to TS1 (**flat**) is the result of the Pd–Ti interaction stabilizing the developing Pd⁰ oxidation state.

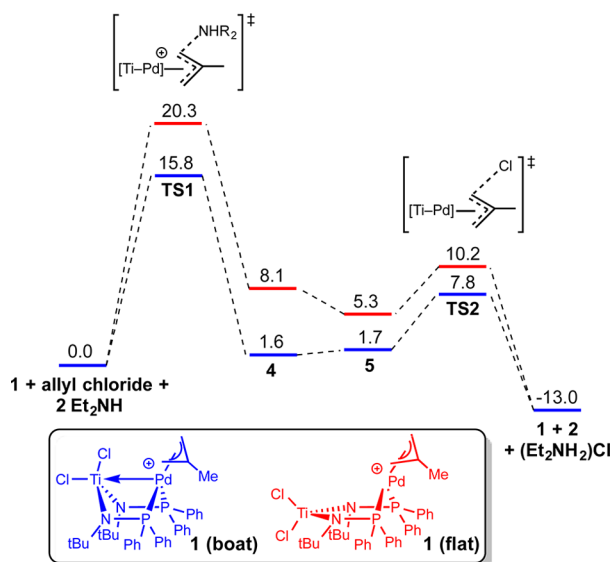


Figure 5. Comparison of allylic amination M06 free energy landscapes catalyzed by **1** (boat) and **1** (flat) (kcal/mol).

From a frontier orbital perspective, the lower barrier is the result of the Pd–Ti orbital interaction causing the Pd–C allyl π^* vacant orbitals to be lowered by ~ 0.1 eV, and this leads to a stronger interaction with the Et_2NH HOMO orbital. These reactivity models are both consistent with Nagashima's proposal that Ti increases the electrophilicity of the Pd(methylallyl) fragment.

The ground-state ΔG between **1** (boat) and **1** (flat) is 13.5 kcal/mol. Replacing the N - t Bu groups with methyl groups results in a boat conformation that is only 2.3 kcal/mol more stable than the flat conformation. The lowest-energy N -Me boat conformation has an elongated Pd–Ti distance of 3.38 Å.¹³ This indicates that the N - t Bu groups are critical to enforce a compact boat ground-state geometry that enables formation of a shorter Pd–Ti interaction in the transition state, which is critical to the low barrier for reductive amine addition (Figure 6). This was confirmed by a calculated $\Delta\Delta G^\ddagger$ of

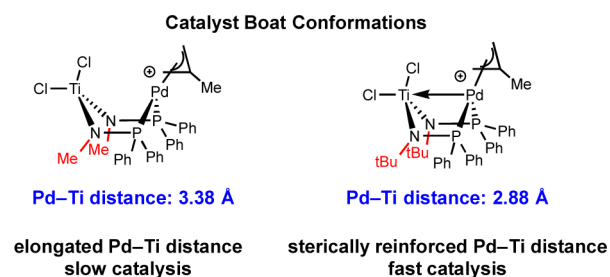


Figure 6. Comparison of ground-state boat conformations and corresponding reactivity for N - t Bu and N -Me.

0.4 kcal/mol for the boat and flat transition states with N -Me groups. As expected, in the boat TS1 for N -Me the Pd–Ti distance is 2.85 Å, which is 0.08 Å longer than TS1 for N - t Bu, and this is apparently not short enough to induce significant transition-state stabilization.

Experimental and Computational Evaluation of the Impact of Replacing TiCl_2 to Remove the Pd–Ti Interaction. As another evaluation of the effect of the Pd–Ti interaction on allylic amination catalytic reactivity, we synthesized and fully characterized the phosphinoamine Pd–methylallyl

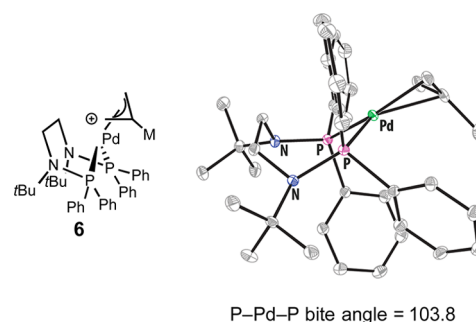
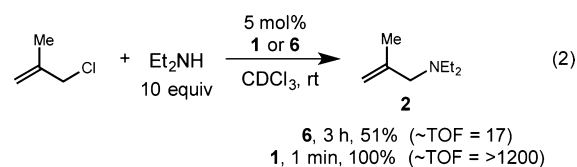


Figure 7. Ethylene bridged bidentate phosphinoamine Pd–Ti complex.

complex **6** (Figure 7). In complex **6**, the phosphinoamine architecture, especially the boat conformation, is maintained when compared to **1**, but the TiCl_2 group is replaced with an ethylene bridge between the nitrogen atoms. Single-crystal X-ray analysis confirmed that complex **6** exists in a boat conformation similar to **1**. The P–Pd–P coordination angle of **6** was also found to differ only slightly from that of **1** (103.8° vs 104.3° for **1**). Complex **6** exhibited only modest catalytic activity in the allylic amination with diethylamine (eq 2, Figure 7), providing $\sim 50\%$ conversion



over the course of 3 h ($\sim\text{TOF} = 17$). In contrast, we found that complex **1** enabled complete amination within <1 min ($\sim\text{TOF} >1200$). This result confirms that the presence of the titanium center contributes to significant rate enhancement in the allylic amination reaction independent of the phosphinoamine ligand structure but does not directly evaluate a through-space versus a through-bond effect.

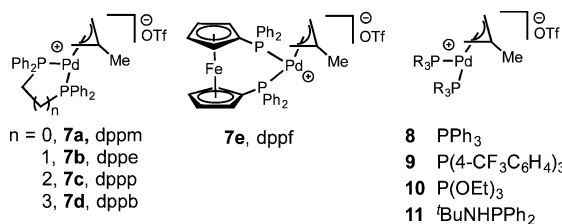
We also investigated with calculations the catalytic cycle for allylic amination with complex **6**. The transition-state geometry for amine addition to catalyst **6** is similar to TS1 and can be found in the Supporting Information. The ΔG^\ddagger is 23.8 kcal/mol. The $\Delta\Delta G^\ddagger$ of 8.0 kcal/mol for TS1 with catalyst **6** compared to catalyst **1** suggests $\sim 10^5$ rate difference, which is in accord with the experimental result reported in eq 2.

Together, these quantitative computational and experimental results support the significance of the Pd–Ti interaction in complex **1** for enhancing the rate of catalysis in allylic amination reactions. Our results confirm that the barrier for turnover-limiting reductive addition of diethylamine to the palladium allyl is significantly lower when the Pd–Ti interaction is intact. Moreover, this key Pd–Ti interaction only occurs as a result of N - t Bu groups enforcing a boat conformation in the ground and transition states during the catalytic cycle.

Impact of Coordination Angle and Electronic Effects on Catalysis. The importance of the Pd–Ti interaction for fast catalysis with complex **1** does not rule out the possibility that a monometallic Pd complex could also have similar reactivity. As discussed earlier, the reactivity comparison of complexes **1** and **3** cannot be interpreted only as the difference between a monometallic and heterobimetallic catalyst. There are also significant ligand and geometry differences between these two catalysts. Therefore, we have also examined the catalytic activity

and transition-state energies for a variety of monometallic systems to ascertain the significance of ligand structure and electronics on the rate of catalysis. To accomplish this aim, we first synthesized a variety of discrete Pd-methylallyl complexes and measured their catalytic efficiency in the amination of methylallyl chloride with diethylamine (Table 1). As a comparison, in our

Table 1. Reactivity Comparison for Monometallic Pd-Catalyzed Allylic Aminations



entry ^a	complex	P–Pd–P angle	time	% conv. ^b	~TOF ^c
1	1	104°	<1 min	100	>1200
2	7a	72°	1 min	48	576
3	7b	86°	12 h	45	0.75
4	7c	95°	12 h	73	1.2
5	7d	99°	1 h	46	9.1
6	7e	101°	6 h	78	2.6
7	8		<1 min	100	>1200
8	9		<1 min	100	>1200
9	10		15 min	71	57
10	11		3 h	50	3.3

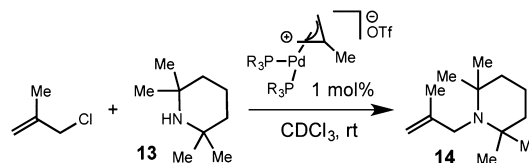
^aReactions performed using 1 mmol methylallyl chloride, 10 equiv of diethylamine, and 0.05 mmol of the indicated preformed allyl complex in CDCl₃ (1 M) for indicated time. ^bDetermined by ¹H NMR analysis of the crude reaction mixture. ^cReported in (mmol product/mmol catalyst)/h.

hands, heterobimetallic complex **1** enabled rapid formation of allyl amine product **2** in 1 min with 5 mol % catalyst loading (entry 1, ~TOF = 1200). Other bis(phosphine) allyl complexes are also catalytically active but with much lower TOFs in most cases (entries 2–6). Bis(diphenylphosphino)methane catalyst **7a** provided the fastest catalysis among the bis(phosphine) ligands surveyed, confirming the importance of the P–Pd–P bite angle to catalyst activity in this allylic amination system.^{14,15}

We also investigated the catalytic activity of bis(monophosphine) palladium complexes and found that in certain cases their catalytic activity was similar to that of **1** (Table 1, entries 8–11). Of the bis(phosphine) complexes tested, bis(triphenylphosphine) complex **8** (Table 2, entry 7) exhibited catalytic activity that was indistinguishable from that of complex **1** under our standard conditions. Complex **8** has a reported P–Pd–P coordination angle^{16,17} that is very similar to that of **1** (105.4° vs 104.3°), suggesting that an optimal coordination angle could be a significant contributor to the exceptional catalytic activity of the bimetallic catalyst. Electron-deficient bis(triarylphosphine) complex **9** led to similar catalysis as with **8** (Table 1, entry 8), while triethylphosphite complex **10** and bis(phosphinoamine) complex **11** led to slower catalysis (entries 9, 11).

Because catalysis in the allylic amination reaction with heterobimetallic complex **1** and bis(triphenylphosphine) complex **8** was kinetically indistinguishable, we calculated the activation barrier for amine addition to each of these complexes. The calculated ΔG^\ddagger for Et₂NH addition (**TS1**) to complex **8** is 21.3 kcal/mol. This reveals that the activation barrier for amine addition to monometallic Pd catalyst **8** is not as low as that for

Table 2. Reactivity of Sterically Hindered Amine **13^a**



entry	complex	time	temp	% conv. ^b	~TOF ^c
1	1	15 min	r.t.	85%	340
2	8	24 h	r.t.	N.R.	–
3 ^d	8	24 h	90 °C	17%	0.7
4 ^d	9	24 h	90 °C	6%	0.2

^aReactions performed using 1 mmol methylallyl chloride, 2.2 equiv of amine, and 0.01 mmol of the indicated preformed allyl complex in CDCl₃ (0.1 M). ^bDetermined by ¹H NMR analysis. ^cReported in (mmol product/mmol catalyst)/h. ^dReaction run at 90 °C in a sealed vial. N.R. = No Reaction.

catalyst **1** and that the similar TOFs reported in Table 1 are due to the inability to measure fast reaction kinetics. In order to support this result, we lowered the catalyst loading to 1 mol % palladium for both catalysts **1** and **8**. While catalyst **1** still provided 100% conversion to product in 1 min, catalyst **8** led to only 28% conversion in 3 min. Thus, the superior catalytic performance suggested by computation of the transition-state energy for amine addition was confirmed in this system.

The success of catalysts **8** and **9** is likely due to an optimal P–Pd–P angle that makes the Pd(η^3 -CH₂C(CH₃)CH₂) fragment electrophilic similar to catalyst **1**. However, a potential alternative explanation for the high catalytic activity of complexes **8** and **9** that is different from **1** is the possibility of triarylphosphine dissociation, which could lead to an unsaturated and more electrophilic Pd metal center. This prompted us to calculate the thermodynamics and activation barriers for unsaturated cationic (PPh₃)Pd(η^3 -CH₂C(CH₃)CH₂) and several other cationic species such as (X)₂Pd(η^3 -CH₂C(CH₃)CH₂) and (X)Pd(η^3 -CH₂C(CH₃)CH₂), where X = chloride or Et₂NH. In all cases, while the thermodynamics for all of these species are viable, they all have larger free energy barriers for Et₂NH addition compared to the transition state with **8**. For example, the free energy barrier for Et₂NH addition to cationic (PPh₃)-(Et₂NH)Pd(η^3 -CH₂C(CH₃)CH₂) is 22.8 kcal/mol and cationic (Et₂NH)₂Pd(η^3 -CH₂C(CH₃)CH₂) is 24.5 kcal/mol. While these are competitive transition states with **8**, they are not lower in free energy.

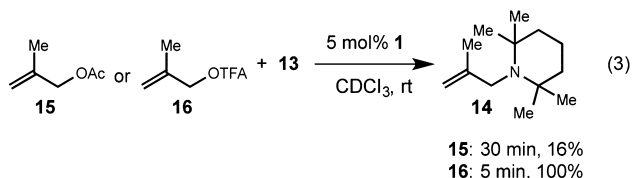
Testing the Limits of the Pd–Ti Interaction. The Michaelis group has previously reported that complex **1** is uniquely active in allylic amination reactions with hindered secondary amine nucleophiles.¹⁸ Because of the intrinsically lower reactivity of 2,2,6,6-tetramethylpiperidine (TMP) (**13**) due to steric strain, slower catalysis should provide the ability to distinguish between the catalytic activity of **1** and **8**. Table 2 reports that catalyst **1** provided 85% conversion to product **14** in 15 min at room temperature with 1% catalyst loading. In contrast, catalyst **8** did not lead to any observable product formation at room temperature, even after extended reaction times (entry 2). When this reaction was heated to 90 °C, complex **8** provided only 17% yield after 24 h (entry 3).¹⁹ Electron-deficient phosphine complex **9** also enabled only modest conversion to product at 90 °C after 24 h (entry 4).

The calculated ΔG^\ddagger for TMP addition to complex **1** is 18.5 kcal/mol. This activation free energy is ~3 kcal/mol higher in free energy than **TS1** for the reaction with Et₂NH.

In contrast, the calculated ΔG^\ddagger for TMP addition to complex **8** is 26.0 kcal/mol. This activation barrier is nearly 4 kcal/mol higher in energy than the transition state for Et₂NH to complex **8** and ~ 7.5 kcal/mol higher than for **1**. Because of the Pd–Ti interaction generates a more reactive allyl species and can stabilize the forming Pd⁰ intermediate, catalysis with **1** is much less sensitive to the sterics of the amine nucleophile, enabling fast catalysis even with highly hindered (and more nucleophilic) substrates. This confirms the unique reactivity of this heterobimetallic catalyst that may be a more general principle for catalyst design.

Allylic acetates are poor substrates for catalysis with **1** and provide low yields in allylic aminations with amine **13**.¹⁸ The poor reactivity of allylic acetates could be caused by the formation of Lewis basic acetate byproducts, which may stimulate catalyst decomposition or deactivation through coordination at titanium. Alternatively, the acetate could serve as a poorer leaving group compared to chloride, causing oxidation by **TS2** to become turnover-limiting and slow for allylic acetates.

In the allylic amination of methallyl acetate (**15**) with 5 mol % catalyst **1**, 16% conversion (~ 3 catalyst turnovers) was observed before reaction progress stalled (eq 3). This suggests that catalyst



decomposition or deactivation indeed occurs before complete conversion is reached. We also calculated the activation barrier for Pd⁰ oxidation of catalyst **1** with allylic acetate **15**. The ΔG^\ddagger for **TS2** is 16.0 kcal/mol higher (23.8 kcal/mol free energy barrier relative to reactants) for **15** than for methallyl chloride, and therefore this reaction step is likely turnover limiting and slow. This illustrates that the heterobimetallic catalyst design can limit the substrate scope if the metal–metal interaction is static along the catalytic cycle. Overall, the poor catalysis with allylic acetates is likely due to a combination of catalyst decomposition and slower catalysis due to slow Pd⁰ oxidation. In contrast, we found experimentally that allylic trifluoroacetates do undergo fast catalysis with **1** (eq 3), presumably due to the lower basicity of trifluoroacetate and the greater ease of Pd⁰ oxidation due to a more stable trifluoroacetate leaving group.

CONCLUSIONS AND OUTLOOK FOR USING HETEROBIMETALLIC COMPLEXES IN ORGANIC REACTION CATALYSIS

The combined experimental and computational results indicate that the fast catalysis in allylic amination reactions with complex **1** is in large part due to the presence of a direct, electron-withdrawing dative interaction between Pd and Ti, independent of electronic properties of the phosphinoamide ligand chassis. A short transition-state Pd–Ti interaction results from the ligand *N*-^tBu groups enforcing a compact boat conformation. Comparison of boat versus flat geometries of catalyst **1** and comparison of **TS1** for catalyst **1** versus catalyst **8** and catalyst **6** provides a range of 10³–10⁵ rate increase due to the Pd–Ti interaction.

This critical transition-state Pd–Ti interaction enables high catalytic efficiency for allylic amination of severely hindered amine nucleophiles under mild reaction conditions.¹⁸ We believe

these results demonstrate the potential of transition-metal–transition-metal interactions to provide distinctively reactive metal complexes via direct interaction between the two metals centers, which effect could have wider impact on catalyst development for organic synthesis. Our results also suggest that a static Pd–Ti interaction can be problematic for catalysis with allylic acetates due slow Pd⁰ oxidation. An ideal solution to make heterobimetallic catalysis more general is designing systems with a dynamic metal–metal interaction along a catalytic cycle.

COMPUTATIONAL DETAILS

All optimizations were performed in Gaussian 09²⁰ with the M06²¹ density functional and 6-31G(d,p)²² basis set for and LANL2DZ²³ pseudopotential/basis set for Pd and Ti ($\Delta E(\text{small})$). All stationary points were confirmed as minima or first-order saddle points by first optimization to a stationary point and then full calculation of the Hessian and vibrational analysis. All optimizations and single-point energies were carried out in the SMD²⁴ CH₂Cl₂ solvent model. All energy calculations were performed with an ultrafine integration grid. Electronic energies were refined using the 6-311+G(2d,p) basis set along with the LAN2TZ(f)²⁵ pseudopotential/basis set for Pd and Ti ($\Delta E(\text{large})$). Free energies are reported at 298 K. Free energies reported are the sum of $\Delta E(\text{large}) + \Delta G_{\text{solv}}(\text{small}) + \Delta E_{\text{ZPE}}(\text{small}) + \Delta H(\text{small}) + nRT - T\Delta S$ correction.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, new compound characterization data, X-ray structure data for complex **6**, *x,y,z* coordinates, and absolute energies of computed structures. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02428.

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Notes

The authors declare no competing financial interest.

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