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Platinum-Catalyzed Intramolecular Hydrohydrazination: Evidence for Alkene Insertion into a Pt−N Bond

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Abstract: Dicationic (bpy)Pt(II) complexes were found to catalyze the intramolecular hydrohydrazination of alkenes. Reaction optimization revealed Pt(bpy)Cl_2 (10 mol %) and AgOTf (20 mol %) in DMF-d_7 to be an effective catalyst system for the conversion of substituted hydrazides to five- and six-membered *N*-amino lactams (*N*-amino = *N*-acetamido at 120 °C, *N*-phthalimido at 80 °C, $^-$OTf = trifluoromethanesulfonate). Of the four possible regioisomeric products, only the product of 5-exo cyclization at the proximal nitrogen is formed, without reaction at the distal nitrogen or 6-endo cyclization. The resting states were found to be a 2:1 Pt-amidate complex (**25**, for *N*-acetamido) of the deprotonated hydrazide and a Pt-alkyl complex of the cyclized pyrrolidinone (**20** for *N*-phthalimido). Both complexes are catalytically competent. Catalysis using **25** as the precatalyst shows no rate dependence on added acid (HOTf) or base (2,6-lutidine). The available mechanistic data are all consistent with a mechanism involving N−H activation of the hydrazide, followed by insertion of the alkene into the Pt−N bond, and finally protonation of the resulting cyclized alkyl complex by hydrazide to release the hydrohydrazination product and regenerate the active Pt-amidate catalyst.

Introduction

Intramolecular hydroamination reactions allow for the facile and efficient formation of nitrogen-containing heterocycles. The hydroamination of alkenes has been studied extensively and found to be effected by a variety of catalysts ranging from (d-block) transition metal and lanthanide catalysts to Brønsted acids and bases.[1] The related amination reactions of alkenes with hydrazines (hydrohydrazinations) remain relatively unexplored despite the potential utility of such a reaction.

The *N*-amino heterocycles that would result from an intramolecular hydrohydrazination reaction are motifs in a number of biologically relevant molecules[2] and are used as chelating ligands for metal-mediated reactions.[3] *N*-Aminopyrrolidines (SAMP and RAMP hydrazines) have also been used extensively as chiral controllers for a variety of transformations, either as auxiliaries (as in the SAMP and RAMP hydrazones)[4] or as components of chiral ligands.[5] Endocyclic dialkyl hydrazines, such as pyrazolidines, have been shown to have biological activity.[6] Additionally, the N−N bond can be cleaved by a variety of methods to generate the corresponding amines, providing an alternate route to the corresponding hydroamination products.[7]

Odom and co-workers have developed a titanium-catalyzed addition of 1,1-disubstituted hydrazines to alkynes to yield the corresponding hydrazones and indoles.[8] Carreira and co-workers have developed a versatile route to alkyl hydrazines from the reductive addition of azodicarboxylates to alkenes.[9] The Rh(I) and Ir(I) hydroamination catalysts developed by Messerle, Field, and co-workers[10] have recently been applied to catalyze the addition of mono- and 1,2-disubstituted hydrazines to alkynes.[11] Additions of hydrazines to dienes have been achieved with a $[Pd(allyl)Cl]_2$ catalyst,[12] and a thermal hydrohydrazination reaction has recently been reported.[13] There are to our knowledge no previous reports of a metal-catalyzed addition of a hydrazine N−H bond to an alkene. We describe here a platinum-

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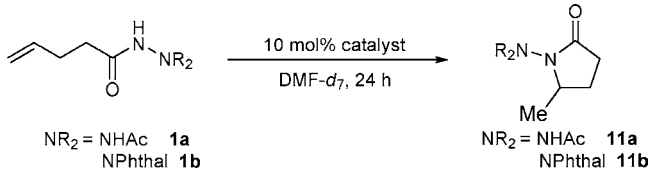
Table 1. Intramolecular Hydrohydrazination of Alkenyl Hydrazides **1a**,**b** Catalyzed by Pt Complexes



		% yield[b]	
entry	catalyst[a]	−NHAc[c] (**11a**)	−NPhthal[d] (**11b**)
1	$Pt(bpy)Me_2$	66	10
2	$[Pt(bpy)(MeCN)_2](OTf)_2$	95−100	76
3	$Pt(bpy)Cl_2$	0	0
4	Pt(ppy)Me(DMSO)	80	30
5	$[Pt(ppy)Cl]_2$	64	15
6	Pt(ppy)Cl(DMSO)	6	35
7	$[Pt(ppy)(MeCN)_2](OTf)$	67	65
8	$[Pt(bph)(SEt_2)]_2$	14	0
9	$Pt(bph)(MeCN)_2$	4	ND[e]
10	$[Pt(MeCN)_4](OTf)_2$	0	0
11	$Pt(PPh_3)_2Cl_2$	0	0

[a] bpy = 2,2′-bipyridine; ppy = cyclometalated 2-phenylpyridine; bph = 2,2′-biphenyldiyl. [b] Determined by ^{1}H NMR. [c] 120 °C. [d] 80 °C. [e] Not determined.

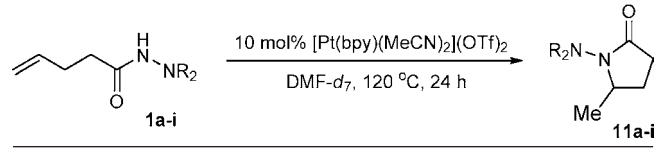
catalyzed intramolecular hydrohydrazination of olefins that likely proceeds through N−H activation of an alkenyl hydrazide followed by olefin insertion into a Pt−N bond.

Results and Discussion

I. Development of Catalytic Hydrohydrazination Reaction. Catalytic Conditions. Our studies began with $Pt(bpy)Me_2$ because it is known to undergo oxidative addition to several heteroatom−heteroatom bonds[14] and because of our interest in the oxidative addition of N−N bonds.[15] Instead of N−N bond cleavage, treatment of alkenyl hydrazide **1a** with 10 mol % $Pt(bpy)Me_2$ results in catalytic cyclization of the hydrazide to the *N*-aminopyrrolidinone **11a**, a net addition of the hydrazide N−H to the alkene. [In this report, compounds **1**−**7** are substrates, **11**−**17** are their respective cyclized products, and **20**−**25** are platinum complexes.] Of the four possible hydrohydrazination products, only a single regioisomer of **11a** is formed. No cyclization of the distal nitrogen was observed, and the proximal nitrogen undergoes 5-exo cyclization exclusively. After investigation of a series of bipyridine (bpy)-, cyclometalated 2-phenylpyridine (ppy)-, and 2,2′-biphenyldiyl (bph)-ligated Pt complexes, we found several other bpy and ppy complexes to be competent catalysts for this hydrohydrazination reaction (Table 1). The highest conversion was observed using $[Pt(bpy)(MeCN)_2](OTf)_2$ as the catalyst ($^-$OTf = trifluoromethanesulfonate). Similar conversions were observed when this catalyst was prepared *in situ* by addition of AgOTf to $Pt(bpy)Cl_2$.

Dimethylformamide (DMF) proved necessary as a solvent. When other polar or high-boiling solvents were employed (DMSO-d_6, CD_3CN, CD_2Cl_2, THF-d_8, toluene-d_8, *p*-dioxane-d_6), low conversion of **1a** to **11a** was observed (0−15% after 10 h at 120 °C), while reactions in DMF-d_7 under the same conditions reached 48% completion. The quality of the DMF was found to be crucial; low water content DMF purchased from ACROS was necessary for reproducibly high conversion.[16]

Table 2. Effect of the Protecting Group on Intramolecular Hydrohydrazination



hydrazide	NR_2	% yield of 11[a]
1a	NHAc	94
1b	NPhthal	20 (76[b])
1c	NHBz	77
1d	NHTFA	100
1e	NHCbz	22
1f	NHBoc	0
1g	NHTs	7
1h	NHPh	16
1i	NMe_2	16

[a] Determined by ^{1}H NMR. [b] 80 °C.

Protecting Groups. Alkenyl hydrazides bearing various protecting groups (**1a**−**i**) were submitted to the optimized catalytic conditions of 24 h at 120 °C in DMF-d_7 with 10 mol % $[Pt(bpy)(MeCN)_2](OTf)_2$ (Table 2). It was found that substrates with an amide protecting group on the distal nitrogen (**1a**−**d**) resulted in the highest yields. The *N*-aminophthalimide substrate (**1b**) decomposes at 120 °C to give predominantly isomerization to internal alkenes, but at 80 °C this isomerization is reduced and much higher conversion to **11b** is obtained within 24 h. Carbamates (**1e**,**f**) and sulfonamides (**1g**) gave much poorer conversion; in the case of the Boc-protected substrate, thermal deprotection was observed. More basic hydrazines, such as alkyl- and aryl-substituted compounds **1h** and **1i**, also gave low conversion (16%). The trifluoroacetamide-protected substrate gave the highest yield but was not chosen for further study due to the instability of $H_2NNHTFA$.[17] Instead we have focused on the acetyl protecting group (**a**) or in some cases phthalimide (**b**) due to its milder reaction and deprotection conditions.

II. Scope of Catalytic Hydrohydrazination Reaction. Synthesis of Hydrazide Substrates. A variety of alkenyl hydrazide substrates were chosen for further study. Hydrazides connected to the alkenyl substituent via an amide linkage (**1**−**6**) were prepared by reaction of the terminal hydrazide ($AcNHNH_2$ (**a**) or $PhthalNNH_2$ (**b**)) with the corresponding acid chloride. The acetyl-protected alkyl hydrazide (**7a**) was generated by nucleophilic addition of $AcNHNH_2$ to the corresponding alkyl bromide. The phthalimide-protected alkyl hydrazide (**7b**) was instead prepared from the condensation of *N*-aminophthalimide with the appropriate aldehyde followed by reduction of the hydrazone to the hydrazine.

Hydrazide Cyclization to *N*-Amino Heterocycles. The standard hydrohydrazination conditions are effective at forming both five- and six-membered ring cyclization products of hydrazides (Scheme 1). The cyclizations to form *N*-aminolactams **11**−**16** proceed without the formation of byproducts, and in most cases complete conversion is achieved within 24 h. Selective conversion to a single regioisomer is observed; no reaction occurs at the distal nitrogen, and no 6-endo cyclization product forms. The more basic hydrazides **7a**,**c** are more challenging substrates.

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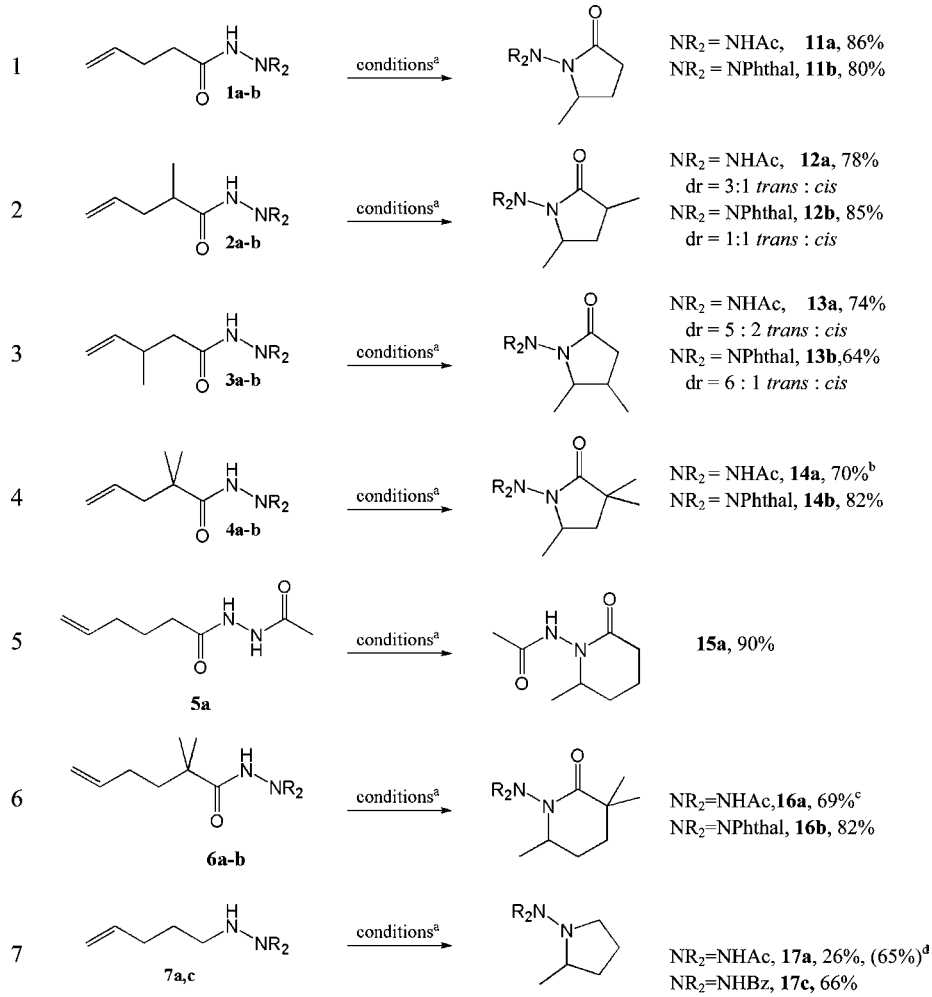
(16) Benchtop solvent, even freshly distilled, resulted in inconsistent yields.
(17) Bredikhin, A.; Túbrik, O.; Sillard, R.; Mäeorg, U. *Synlett* **2005**, 1939–1941.

Scheme 1. Intramolecular Hydrohydrazination To Form *N*-Amino Heterocycles



[a] Yields given are isolated yields after 1 day unless otherwise noted. $Pt(bpy)Cl_2$ (10 mol %); AgOTf (20 mol %); DMF; $T = 80$ °C when NR_2 = NPhthal, 120 °C when NR_2 = NHAc. [b] 2 days. [c] Reaction mixture was resubmitted to reaction conditions to obtain complete conversion. [d] Percent conversion by ^1H NMR.

The conversions of **7a**,**c** to **17a**,**c** reach only ~70% with 10 mol % catalyst. Surprisingly, longer reaction times (2 days) and higher catalyst loadings (20 mol %) do not improve conversion. In addition, the phthalimide-protected analogue, **7b**, shows no reaction under the hydrohydrazination conditions.

The poor yield of *N*-acetamidopiperidine product **17a** is due to difficulty in separating it from starting hydrazide by silica column chromatography. The benzoyl protected analogue (**17c**) did not suffer from this problem. The thermal hydrohydrazidation of **7c** has recently been reported,[13] and the Pt-catalyzed conditions reported here appear to provide no significant improvement over the thermal conversion of hydrazides with an amine-type linker (Scheme 1, entry 7). The hydrazides with an amide-type linker, however, do not undergo thermal cyclization; no conversion of **1a** is achieved in the absence of a Pt catalyst after 1 day at 120 °C in DMF-d_7.

Both longer chains (*N*-acetamidoheptenamide) and internal alkenes (*N*-acetamido- and *N*-phthalimido-4-hexenamide) are unreactive under these conditions, in addition to the *N*-acetamidoallyl carboxamide. The related amines (such as *N*-benzyl-4-pentenamide) do not cyclize to the pyrrolidine under these conditions, suggesting that this reaction may be unique to hydrazides.

The protecting group on the distal nitrogen appears to have some influence on the diastereoselectivity of the cyclization, as indicated by products **12** and **13**. The diastereomers were assigned by 2D COSY and NOESY analyses (Figures S1−S9), and the ratios determined by ^1H NMR spectroscopy and GC-MS. In almost all cases, we found the *trans* isomer to be favored, with ratios varying from 1:1 to 3:1 for **12** and from 2.5:1 to 6:1 for **13** depending upon the choice of $-NR_2$. The influence of protecting groups on diastereoselectivity has been observed in the formation of pyrazoles where cyclization occurs at the protected distal nitrogen.[18] The related effect observed in the formation of these *N*-amino lactams in which the relevant protecting group is on an exocyclic nitrogen is less pronounced.

The *N*-amidopyrrolidinones and *N*-phthalimidopyrrolidinones can be deprotected to give the free *N*-aminopyrrolidinones (see Supporting Information).[19]

III. Isolation and Characterization of Platinum Complexes. A number of platinum complexes have been isolated as part of efforts to understand the mechanism of hydrohydrazination. The synthesis and characterization of platinum-alkyl complexes and

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(19) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637–640.

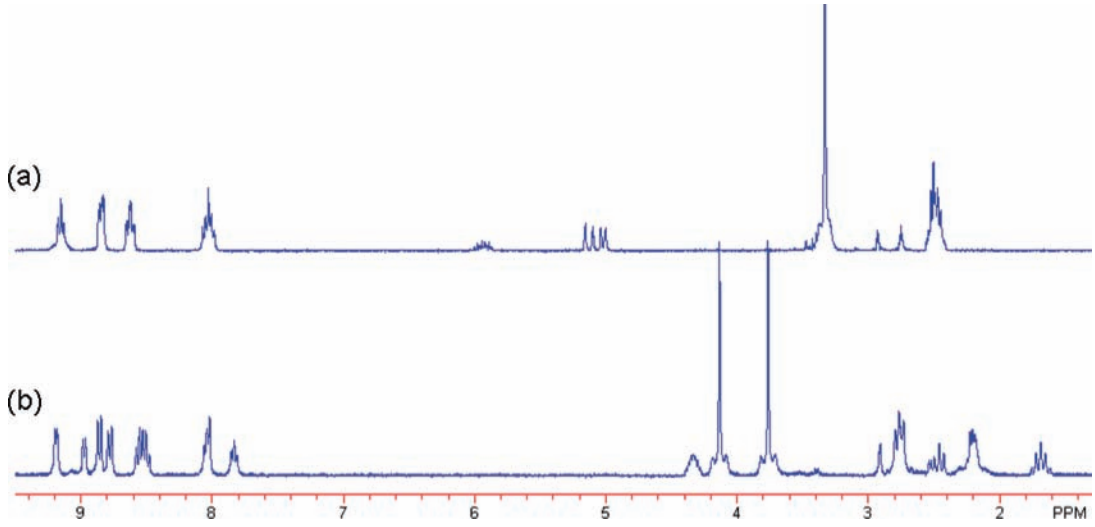
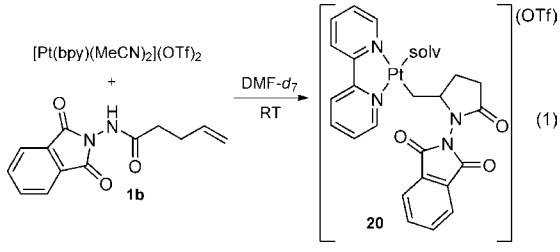


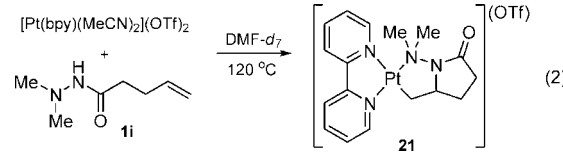
Figure 1. ^{1}H NMR spectra of (a) Pt-amidate complex **23** and (b) Pt-alkyl complex **21** in DMF-d_7 at 300 MHz.

then -amidate complexes are described, as well as the potential involvement of these species in the catalytic cycle(s).

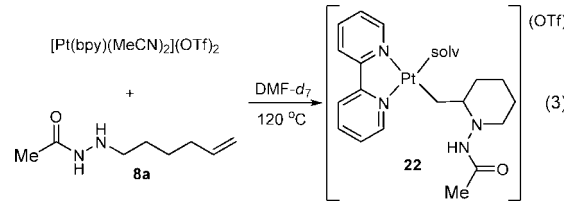
A. Platinum Alkyl Complexes. [(bpy)Pt(CH$_2$CH(CH$_2$)$_2$C(O)N-NPhthal)(CD$_3$CN)](OTf) (20). The reaction of [Pt(bpy)(MeCN)$_2$](OTf)$_2$ and **1b** in DMF-d_7 at 80 °C forms a new Pt-alkyl complex (**20**) as the sole platinum species observed in solution under both catalytic and stoichiometric conditions (eq 1). Complex **20** is also formed on treatment of [Pt(bpy)(MeCN)$_2$](OTf)$_2$ with **1b** in DMF-d_7 at room temperature, and no intermediates are observed. Complex **20** has the expected ^{1}H NMR spectrum for a complex with an unsymmetrical Pt center with key resonances including a characteristic methine multiplet at 4.1 ppm in addition to an upfield methylene signal (δ = 1.47) that displays coupling to Pt (J_{PtH} = 69 Hz). The couplings and connectivity of these signals, as indicated by 1D ^{1}H NMR and 2D COSY experiments, are consistent with the assignment of **20** as the Pt-alkyl complex shown in eq 1. The presence of a $^-$OTf anion was confirmed by ^{19}F NMR spectroscopy (δ = −79.5 ppm). ESI-MS analysis (CH$_3$CN) shows the expected mass (m/z = 594) and isotope pattern for **20** with loss of solvent.



[(bpy)Pt(CH$_2$CH(CH$_2$)$_2$C(O)N-N(CH$_3$)$_2$)](OTf) (21). Heating [Pt(bpy)(MeCN)$_2$](OTf)$_2$ with *N*,*N*-dimethylaminohydrazide **1i** at 120 °C in DMF-d_7 also results in formation of a Pt-alkyl complex (**21**), similar to **20** but with the chelating dimethylamino group taking the place of solvent (eq 2). Like **20**, the ^{1}H NMR spectrum of **21** shows the expected bpy and methylene resonances, and the characteristic methine multiplet at 4.34 ppm. In addition, there are two diastereotopic methyl groups each with distinct Pt-satellites (4.14 and 3.77 ppm, $^3J_{PtH}$ = 14.7 and 14.1 Hz, Figure 1b), indicating that the dimethylamino group is coordinated to Pt. The ^{19}F NMR spectrum (δ = −79.6 ppm) and ESI-MS (m/z = 492) analysis are consistent with this assignment of **21**. These resting states **20** and **21** are analogous to those observed in Pt- and Pd-catalyzed hydroamination systems, which involve protonation of a metal-alkyl species to release the cyclized hydroamination product.[20]



A related Pt-alkyl metallacycle (**22**) has been isolated from the catalytic reaction mixtures of hydrazide **8a**. The cyclized hydrohydrazination product appears to be formed in good yield (60−70% yield) by ^{1}H NMR spectroscopy but, like **17a**, could not be purified by silica column chromatography. Complex **22** has been characterized by ^{1}H, ^{19}F, and 2D COSY NMR spectroscopies. The ^{1}H NMR spectrum of **22** shows the characteristic methine resonance (δ = 4.2 ppm), eight diastereotopic methylene proton resonances, and a broad singlet at 11.2 ppm suggestive of an N*H*. The ESI-MS analysis (m/z = 506) is consistent with a monocation of this type. All of the data indicate a Pt-alkyl complex as shown in eq 3. Unlike **20** and **21**, which are formed from alkenyl hydrazide **1** with the amide linker, **22** is the Pt-alkyl complex formed from an alkenyl hydrazide with an amine linker. Complex **22** is the predominant Pt species in solution during the catalytic reaction of **8a** when monitored by ^{1}H NMR spectroscopy.



Catalytic Activity of [(bpy)Pt(CH$_2$CH(CH$_2$)$_2$C(O)N-N(CH$_3$)$_2$)](OTf) (20). Complex **20** is a competent catalyst for the hydrohydrazination reaction. Heating a solution of isolated **20** with

(20) (a) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070–1071. (b) Cochran, B. M.; Michael, F. E. *J. Am. Chem. Soc.* **2008**, *130*, 2786–2792.

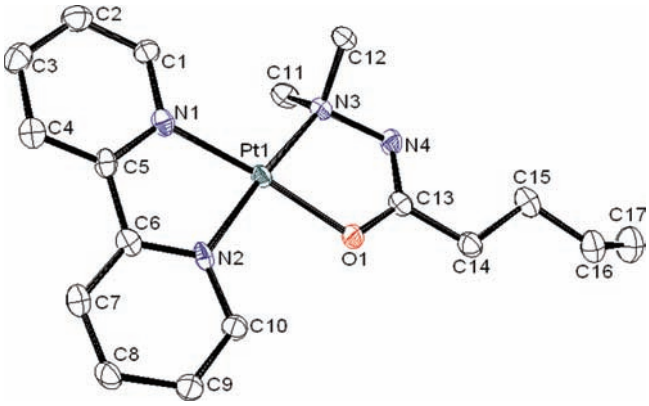


Figure 2. ORTEP of $[Pt(bpy)(\kappa^2\text{-}Me_2NN{=}C(O)(CH_2)_2CH{=}CH_2)]^+$, the cation of **23**, with 50% probability ellipsoids. The triflate counterion was omitted for clarity.

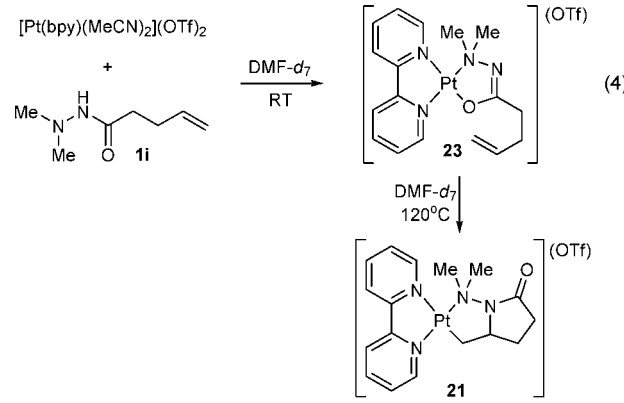
Table 3. Selected Bond Distances (Å) and Angles (deg) in **23**

Pt1−O1	1.980(3)	O1−Pt1−N3	173.87(16)
Pt1−N3	2.034(4)	O1−C13−N4	125.3(5)
N3−N4	1.497(6)		
O1−C13	1.312(6)		
N4−C13	1.295(7)		
C16−C17	1.304(8)		

10 equiv of **1b** under the typical reaction conditions (DMF-d_7, 80 °C) results in 70% conversion of **1b** to **11b** after 24 h. Treatment of **20** with HOTf (2 μL, 3 equiv) results in formation of **10b** in ~25% yield after 3 days at 80 °C, with isomerization of **1b** to the α,β-unsaturated hydrazide accounting for the remaining organic material. Although significant isomerization is not observed under the chosen catalytic conditions (80 °C), it has been observed under more forcing conditions (120 °C, see Section I). Additionally, treatment of **20** with the hydrazide AcNHNHAc[21] (40 equiv) results in formation of **11b** and isomerization of **1b** to the α,β-unsaturated hydrazide (1:1 ratio) and complete conversion of **20** to the amidate complex **24** (see below) after 24 h heating at 80 °C in DMF-d_7. These data suggest that turnover from **20** is capable of proceeding through protonation by the hydrazide **1b**.

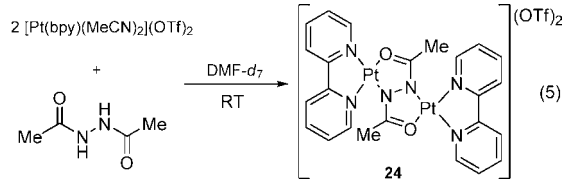
B. Platinum Amidate Complexes. $[Pt(bpy)(\kappa^2\text{-}Me_2NN{=}C(O)(CH_2)_2CH{=}CH_2)](OTf)$ (23). To obtain insight into the reaction mechanism prior to metallacycle formation, mixtures of $[Pt(bpy)(MeCN)_2](OTf)_2$ and **1i** in DMF-d_7 were monitored by ^{1}H NMR spectroscopy at RT (**21** forms at 120 °C). Within minutes, complete conversion to a single Pt species (**23**) is observed. Complex **23** was obtained cleanly by precipitation with ether. The ^{1}H NMR spectrum of **23** shows eight bpy resonances, terminal and internal alkene resonances (4.98 and 5.85 ppm in DMF-d_7) that are only slightly shifted from those of the free hydrazide (5.00 and 5.86 ppm in DMF-d_7), two methylene resonances, and a single Pt-CH_3 signal (δ = 3.32, J_{PtH} = 11 Hz, Figure 1a). No N*H* proton is observed, and ESI-MS analysis (m/z = 492) indicates **23** to be isomeric with **21**.

These data indicate that **23** is the Pt(amidate) monocation with a chelating deprotonated hydrazide as shown in eq 4. X-ray analysis performed on crystals grown from a DMF-d_7/ether solution at −37 °C confirms this assignment (Figure 2, Tables 3 and S-1). The presence of a single OTf^- counterion in addition to the double-bond character of C13−N4 (1.295 (7) Å) confirm the deprotonation of N4.



Heating isolated **23** in DMF-d_7 results in slow conversion to **21** over the course of 2 weeks at 120 °C (eq 4). When **23** is added to a catalytic hydrohydrazination reaction of **1i** in progress, the conversion of **23** to **21** is much faster (complete conversion in <1 h). This appears to indicate that this process is accelerated by the presence of hydrazide or acid. This could be consistent with acid-promoted tautomerization to the N-bound Pt(amidate) followed by insertion of the alkene as a possible pathway to **21**.

$[(bpy)_2Pt_2(AcNNAc)](OTf)_2$ (24) and $[(bpy)_2Pt_2(AcNNC(O)CH_2CH_2CH{=}CH_2)](OTf)_2$ (25). 1,2-Diacetyl hydrazide (AcNHNHAc) reacts slowly with $[Pt(bpy)(MeCN)_2](OTf)_2$ in DMF-d_7 at RT. After ~15 h, ^{1}H NMR spectra showed complete conversion to a new Pt species (**24**, eq 5), which was precipitated from solution with ether. The ^{1}H NMR spectrum of **24** indicates incorporation of 1 hydrazide per 2 (bpy)Pt fragments. No N*H* or hydride resonances are observed. ESI-MS analysis (CH_3CN) shows a prominent ion with two (bpy)Pt units per hydrazide (m/z = 965), with an isotope pattern consistent with $[Pt_2bpy_2(AcNNAc)(OTf)]^+$. All of these data are consistent with a 2:1 complex with C_{2h} symmetry in which each bpy ligand is asymmetric (eq 5). This coordination mode has been observed for monomeric phosphine-ligated Pt complexes of hydrazides.[22]

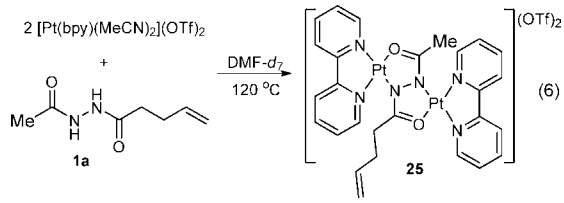


Similarly, heating a mixture of $[Pt(bpy)(MeCN)_2](OTf)_2$ and **1a** at 120 °C in DMF for 30 min results in the formation of the analogous 2:1 complex **25** (eq 6). The ^{1}H NMR spectrum of **25** shows 16 aryl resonances (from two asymmetric and inequivalent bpy ligands), terminal alkene resonances, two methylene resonances, and an acetyl methyl resonance; no N*H* signals are observed. The alkene resonances are only slightly shifted (5.05 and 5.92 ppm in DMF-d_7) from those of the free hydrazide (4.99 and 5.87 in DMF-d) and show no coupling to Pt. ^{19}F NMR (δ = −79.8 ppm) confirms the presence of triflate counterions. The masses (m/z = 1005, 428) and isotope pattern observed by ESI-MS analysis are consistent with the formulation of **25** as a

(21) AcNHNHAc was used because it is similar to the substrates but allows for cleaner ^{1}H NMR differentiation from the phthalimide Pt complex **20**.

(22) Dilworth, J. R.; Kasenally, A. D. *J. Organomet. Chem.* **1973**, *60*, 203–207.

2:1 complex. These data together indicate **25** to be a 2:1 complex with C_s symmetry as shown in eq 6.

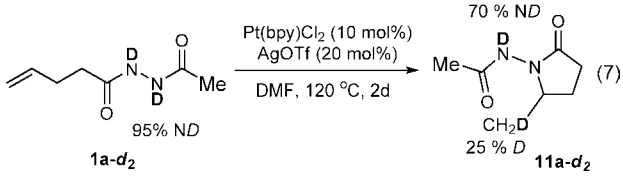


Complex **25** is the predominant Pt species observed in solution by ^{1}H NMR spectroscopy during the catalytic conversion of **1a** to **11a**. When isolated **25** is treated with **1a** (15 equiv), complete conversion to **11a** is observed after 24 h at 120 °C. Attempts to observe formation of a Pt-alkyl species analogous to **20** and **21** have been unsuccessful. Heating a solution of isolated **25** at 80 °C in DMF-d_7 results in consumption of **25** and formation of **11a** after 2 days. The proton required to convert **25** to **11a** could be derived from trace water in the solvent or even the bpy ligand.[23] Heating solutions of **25** in CD_3CN or CD_2Cl_2 similarly gives only **11a**, while in THF-d_8 no reaction occurs.

Treatment of isolated **24** with alkenyl hydrazide **1a** also gives complete conversion to cyclized product **11a**. Heating a mixture of the pentenoic hydrazide resting state **25** and the *hexenoic* hydrazide **5a** results in formation of both five- and six-membered rings (**11a** and **15a**, distinguishable by ^{1}H NMR) and a mixture of the two corresponding platinum amidate complexes even at early reaction times (<1 h). These data suggest a rapid equilibrium between the Pt-amidate complex **25** and the alkenyl hydrazide.

The 2:1 Pt-amidate complexes, like **25**, are the resting states observed in catalytic reaction mixtures of the diacyl hydrazides **1a**−**6a**. In the case of the disubstituted hydrazides (**1b**, **1i**) and those with an amine-type linker (**7**−**8a**), a Pt-alkyl complex is the observed resting state. These resting states likely reflect the relative stabilities of the corresponding Pt-amidate complexes.

C. Reaction Dependence on Acid and Base. Heating the deuterated hydrazide **1a-*d*$_2$** (95% N*D*) in DMF or DMF-d_7 with Pt(bpy)Cl_2 (10 mol %) and AgOTf (20 mol %) for 2 days leads to complete consumption of **1a-*d*$_2$** (eq 7). The cyclized product **11a** formed has substantial deuterium incorporation in the amide group, ∼70% N*D* by ^{1}H NMR, and some incorporation of deuterium into the exocyclic methyl group (∼25% D by ^{1}H NMR). The positions of deuterium incorporation were confirmed by ^{2}H NMR spectroscopy. The incomplete deuterium incorporation is likely due to exchange with trace H_2O present in the solvent prior to protonation of the Pt−alkyl bond.



Experiments were done to probe the role of acid and base in the catalytic process. $PhSiMe_3$ has been shown to be a valuable probe of Brønsted acid catalysis in hydroamination by quickly reacting with HOTf and inhibiting any acid-catalyzed processes.[24] Addition of $PhSiMe_3$ (1 equiv) to the catalytic reaction of **1a** in DMF-d_7 at 120 °C results in no change in the rate of conversion to **11a** (i.e., 100% after 15 h) and no consumption of $PhSiMe_3$, indicating that hydrohydrazination is not simply a Brønsted acid-catalyzed process. To further probe the role of acid and base in the catalytic process, a solution of isolated **25** and **1a** (10 equiv) in DMF-d_7 was divided into three equal portions in three J. Young tubes. To one tube was added HOTf (9 equiv), and to another was added 2,6-lutidine (2.5 equiv); all three tubes were sealed, heated in a 120 °C oil bath, and monitored periodically by ^{1}H NMR spectroscopy. The three solutions were found to undergo conversion of **1a** to **11a** at similar rates (Figure S10), showing no significant acceleration or inhibition of the formation of **11a** by either acid or base. In conjunction with the turnover experments from Section IIIA (see above), these data suggest that the hydrazide is responsible for the protonolysis of alkyl complex **20** rather than HOTf.

IV. The Mechanism of Hydrohydrazination. The Pt complexes synthesized and characterized above, and their behavior under catalytic conditions, provide insight into the mechanism of catalysis. In this section, we use those results to consider the likely mechanisms for hydrohydrazination, in particular the key C−N bond forming step: nucleophilic attack of the hydrazide at the alkene (mechanism A) or alkene insertion into a Pt−N bond (mechanism B, Scheme 2).

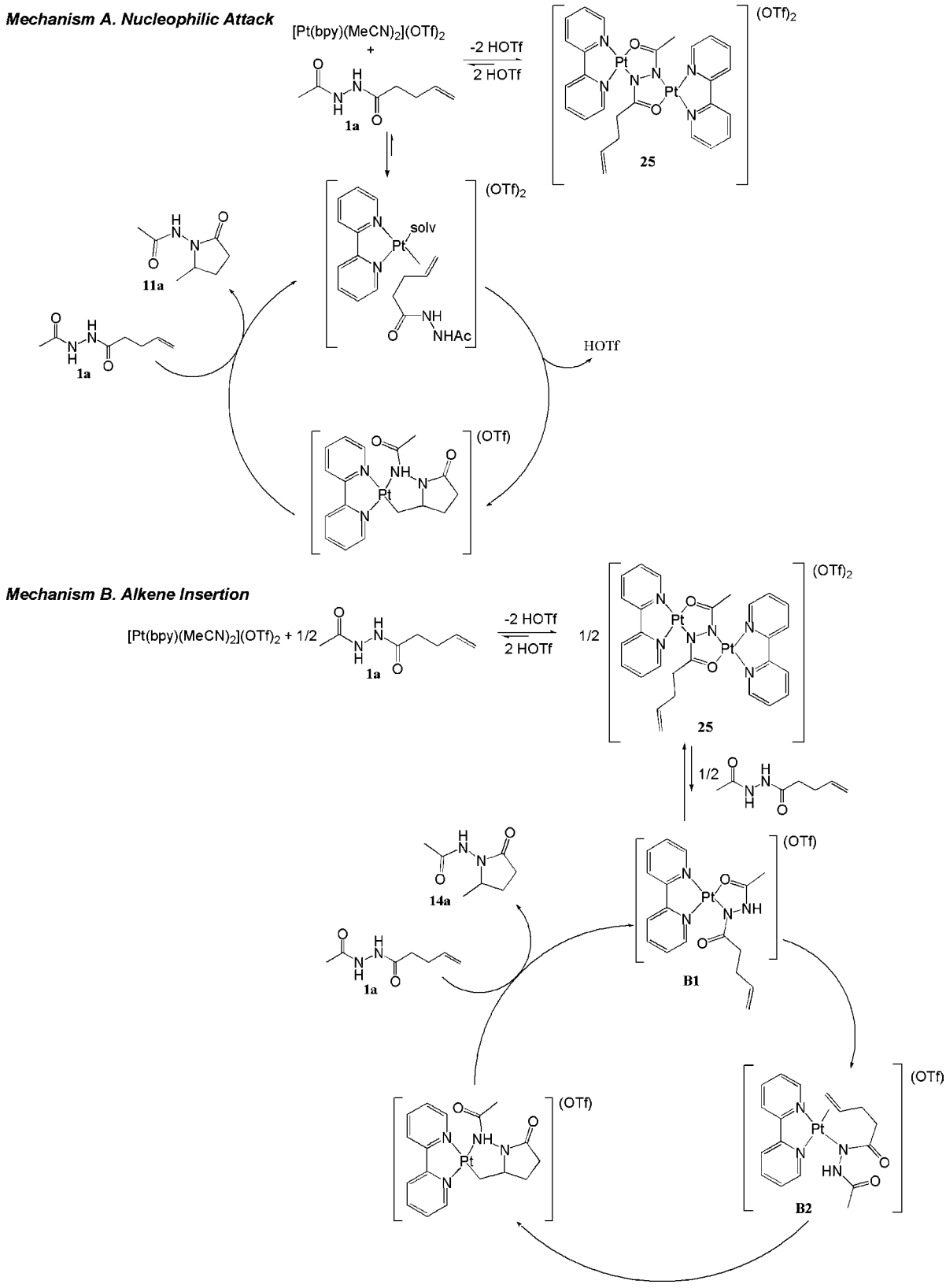
A. Nucleophilic Attack Mechanism. In many hydroamination and related reactions, the alkene is activated toward attack by an external nucleophile by coordination to a metal center.[1,20] For the hydrohydrazination reaction discussed here, this would likely involve intramolecular attack of an unbound hydrazine connected to a coordinated alkene. The predominant Pt species in solution during catalytic hydrohydrazination of **1a** is the 2:1 complex **25**. In order for this nucleophilic pathway to be the operative mechanism, **25** must access a catalytic cycle such as mechanism A in Scheme 2. Specifically, **25** must be converted to a platinum-alkene with a free hydrazine, which requires protonation of the amidate complex. However, the rate of conversion of **1a** to **11a** catalyzed by **25** under these conditions shows no acid (HOTf) or base (2,6-lutidine) dependence. In general, conversion of the amide complex to an alkene complex that would be susceptible to nucleophilic attack would require acid. Therefore the lack of acid catalysis and base inhibition appears to be inconsistent with a nucleophilic attack of a hydrazine on a bound alkene. The exchange observed between the amidate complex **25** and the hexenamide substrate **5a** likely proceeds by proton transfer from one amide to another, without accessing the (bpy)Pt(solv)$_2^{2+}$ precatalyst, which would appear to be needed for the nucleophilic attack mechanism.

An alternative nucleophilic attack mechanism could in principle involve addition of an anionic hydrazide to a bound alkene, which would not require acid. However, hydrazide is a very poor leaving group, and displacement from the platinum, either dissociatively or associatively by the alkene, is highly unlikely. An O-bound acyl hydrazide, as in **23**, could serve as a nucleophile but not to an alkene bound to the same metal center due to ring constraints. Attack of an O-bound acyl hydrazide on its pendant alkene bound to a different metal center is more difficult to exclude on steric grounds, but it would require that the C−N bond forming step be zero-order in alkenyl hydrazide. A brief kinetic study of the reaction of the diplatinum

(23) Minghetti, G.; Stoccoro, S.; Cinellu, M. A.; Soro, B.; Zucca, A. *Organometallics* **2003**, *22*, 4770–4777.

(24) This takes place in 1 h at room temperature; see: McBee, J. L.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2008**, *130*, 16562–16571.

Scheme 2. Possible Mechanisms of Pt-Catalyzed Hydrohydrazination



complex **25** with **1a** suggests a half-order dependence on the [alkenyl hydrazide] (Figure S11). Such a half-order dependence suggests dissociation of the dimer by reaction with **1a** and a unimolecular C−N bond forming step, and therefore argues against a dinuclear nucleophilic attack pathway.

B. Alkene Insertion Mechanism. The available mechanistic data suggest that Pt-amidate species directly convert to Pt-alkyl complexes. When NR_2 is *N*-acetamido, this conversion occurs through reaction of the amidate resting state **25** with hydrazide **1a** to give **B1** as shown in Scheme 2. In the case where NR_2 is

N-dimethylamino, conversion of the Pt-amidate complex (**23**) to the Pt-alkyl resting state (**21**) requires tautomerization from the O-bound to an N-bound amidate and dissociation of the chelating amine and coordination of the alkene. This would give a species analogous to **B2** that is well set up for alkene insertion to give **21**.

These conversions of Pt(amidate) to Pt(alkyl) would not need to require acid. The half-order dependence on [alkenyl hydrazide] is consistent with a mechanism in which the hydrazide **1a** protonates the diplatinum hydrazide(2−) catalyst resting state **25**. This forms the 1:1 amidate complex in the catalytic cycle, shown as **B1** in mechanism B of Scheme 2. Complex **B1** could then rearrange to an alkene-bound isomer (**B2**) and undergo alkene insertion into the Pt−N bond to give a platinum alkyl complex similar to **20**, **21**, and **22**.

Several late metal systems have been shown to undergo stoichiometric or catalytic insertion of alkenes into M−N bonds. These include Ir bis(phosphine) systems that promote the amination of norbornene[25] and an amido transfer reaction from Rh(amido) complexes that involves alkene insertion into the Rh−N bond.[26] Although the stoichiometric insertion of activated olefins into Pt−N bonds has been reported,[27] few Pt-catalyzed amination reactions have been shown to proceed through alkene insertion into a Pt−N bond. This mechanism, however, has been proposed in several Pd-catalyzed amination reactions.[28] Obtaining direct evidence of an alkene insertion pathway is challenging. We have attempted to observe both intra- and intermolecular insertions into the isolated Pt-amidate complexes **24** and **25**. Heating isolated **25** forms **11a** without any observable intermediates; the proton source is unclear. Intermolecular reactions of **24** with both activated (acrylonitrile, methyl vinyl ketone, norbornene) and unactivated (propene, hexene, dodecene) alkenes in DMF-d_7 do not lead to olefin incorporation products.

The cycle is completed with protonation of the Pt-alkyl complex by an additional molecule of alkenyl hydrazide substrate. The isolated Pt-alkyl complexes **20** and **21** are the only resting states observed that lie in the catalytic cycle, implying protonolysis of the Pt-alkyl complex is turnover limiting. Protonation of a metal alkyl species is a common step in Pd- and Pt-catalyzed hydroamination reactions.[20] In our system, the HOTf formed during the reaction is not solely responsible for the final protonation of the Pt(alkyl) complex since the reaction is unaffected by the addition of $PhSiMe_3$ as an acid trap. The *N*-phthalimidopyrrolidinone **11b** can be released from the Pt-alkyl complex **20** by protonation with AcNHNHAc, confirming that the hydrazides employed in these reactions are acidic enough to protonate a Pt-alkyl species.

Conclusions

Dicationic (bpy)Pt(II) complexes catalyze the intramolecular hydrohydrazination of hydrazides to form five- and six-membered *N*-amino lactams. A number of platinum complexes have been isolated from these reaction mixtures and shown to be relevant to the catalytic process. Addition of acid (HOTf) or base, or an acid scavenger, has little effect on the rate of reaction. On the basis of these data and catalytic and stoichiometric reactions of the isolated intermediates, we suggest a mechanism that involves N−H activation of the hydrazide, followed by insertion of the alkene into the Pt−N bond. Protonation of the resulting Pt−C bond in the cyclized alkyl complex by a hydrazide releases the hydrohydrazination product and regenerates the catalytically active Pt-amidate species. An alternative pathway of external attack of the hydrazide on a bound alkene is difficult to rationalize with the limited effect of added acid or acid scavengers.

Experimental Section

General Procedures. All procedures were done air-free with glovebox or vacuum line techniques unless otherwise noted. ^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} NMR spectra were recorded on Bruker Avance 300 or 500 MHz spectrometers and referenced to the residual solvent signal (^{1}H and ^{13}C) or an external CF_3COOH standard ($^{19}F = -78.5$);[29] all coupling constants are reported in Hz. Infrared spectra were measured on a Perkin-Elmer spectrum RX I spectrometer. Mass spectra were collected on an a Bruker Esquire 1100 liquid chromatograph−ion trap mass spectrometer or an Agilent 5973 gas chromatograph−mass spectrometer. Column chromatography was performed using silica gel (Whatman, 60 Å, 230 × 400 mesh). High-resolution mass spectra were collected on a JEOL HX-110 mass spectrometer.

Materials. All commercial reagents were used as received unless otherwise noted. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. CD_2Cl_2 was dried over CaH_2 and distilled before use. THF-d_8 was distilled from Na/benzophenone before use. Toluene-d_8 was dried over Na/K and distilled before use. CD_3CN was dried over a sequence of CaH_2, P_2O_5, and CaH_2. DMF-d_7 and dioxane-d_8 were used without further purification. K_2PtCl_4 was purchased from Pressure Chemical.

General Procedure for the Catalytic Hydrohydrazination Reaction. Reactions were prepared in an N_2 glovebox. Acros low water (<50 ppm) DMF was used; other drying and purification methods yielded irreproducible yields. A sealed tube was charged with hydrazide (1 equiv), Pt(bpy)Cl_2 (0.1 equiv), AgOTf (0.2 equiv), and DMF (0.16 M). The reaction mixture was submerged in an oil bath (120 °C for substrates **a** and **c**, 80 °C for substrates **b**) for 1 day (unless otherwise indicated). After removal of the solvent *in vacuo*, the product was purified by silica column chromatography using the solvent system listed with each compound.

***N*-Acetamido-2-methylpyrrolidin-5-one (11a).** Reaction of **1a** (36 mg, 230 μmol) with Pt(bpy)Cl_2 (10 mg, 24 μmol) and AgOTf (12 mg, 47 μmol) in DMF (1.4 mL) followed by silica column chromatography with 10% MeOH in CH_2Cl_2 provided **11a** as a colorless oil (31 mg, 86%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.45 (s, 1H, N*H*), 4.03 (m, 1H, C*H*), 2.45 (m, 2H, CH_2), 2.32 (m, 1H, CH_2), 2.06 (s, 3H, AcCH_3), 1.68 (m, 1H, CH_2) 1.21 (d, $J = 6.5$ Hz, 3H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 174.5 (*C*O), 169.6 (*C*O), 54.8, 28.5, 25.6, 20.9, 19.2. FTIR (thin film, cm^{-1}): 3423, 3232, 1702, 1655, 1537, 1419, 1378, 1270. ESI-MS (MeOH, *m*/*z*): 179 $[M + Na]^+$ (8), 195 $[M + K]^+$ (1). HRMS (FAB): calcd for $C_7H_{13}N_2O_2$ $[M + H]^+$ *m*/*z* 157.09770, found *m*/*z* 157.09783.

***N*-Aminophthalimido-2-methylpyrrolidin-5-one (11b).** Reaction of **1b** (46 mg, 188 μmol) with Pt(bpy)Cl_2 (8 mg, 19 μmol) and AgOTf (10 mg, 39 μmol) in DMF (1.2 mL) followed by silica

(25) (a) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738–6744. (b) Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220–12221.
(26) Zhao, P. J.; Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 12066–12073.
(27) (a) Cowan, R. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4750–4761. (b) Villanueva, L. A.; Abboud, K. A.; Boncella, J. M. *J. Am. Chem. Soc.* **1992**, *11*, 2963–2965.
(28) (a) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763–773. (b) Ney, J. E.; Wolfe, J. P. *Angew. Chem.* **2004**, *116*, 3689–3692. (c) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328–6335.
(29) Walstrom, A.; Pink, M.; Tsvetkov, N. P.; Fn, H.; Ingleson, M.; Caulton, K. G. *J. Am. Chem. Soc.* **2005**, *127*, 16780–16781.

column chromatography with 3:2 hexanes/EtOAc provided **11b** as a white solid (37 mg, 80%), mp 164 °C. ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 7.90 (m, 2H, Ar), 7.82 (m, 2H, Ar), 4.05 (m, 1H, C*H*), 2.52 (m, 2H, CH_2), 2.41 (m, 1H, CH_2), 1.85 (m, 1H, CH_2), 1.25 (d, J = 4 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (CD_2Cl_2, 125 MHz): δ 173.1 (*C*O Ac), 165.2 (*C*O phthal), 165.0 (*C*O phthal), 134.9 (Ar), 134.8 (Ar), 130.3 (Ar), 130.00(Ar), 124.2 (Ar), 124.0 (Ar), 55.3, 28.3, 26.1, 19.5. FTIR (thin film, cm^{-1}): 1736 (s), 1720 (s), 1353, 1249, 1113, 1085, 881, 712. ESI-MS (MeOH, *m*/*z*): 163 (8), 245 [M + H]$^+$ (1), 277 (3), 299 (10), 315 (8). HRMS (FAB): calcd for $C_{13}H_{13}N_2O_3$ [M + H]$^+$ *m*/*z* 245.09262, found *m*/*z* 245.09272.

***N*-Acetamido-3,5-dimethylpyrrolidin-2-one (12a).** Reaction of **2a** (20 mg, 118 μmol) with Pt(bpy)Cl_2 (6 mg, 14 μmol) and AgOTf (6 mg, 23 μmol) in DMF (0.75 mL) followed by silica column chromatography with 10% MeOH in CH_2Cl_2 provided **12a** as a mixture of diastereomers (1:3 *cis*:*trans*), colorless oil (16 mg, 78%). ^{1}H NMR (C_6D_6, 500 MHz): δ 9.77 (s, 1H, N*H*, *trans*), 9.64 (s, 1H, N*H*, *cis*), 3.93 (m, 1H, C*H*, *trans*), 3.88 (m, 1H, C*H*, *trans*), 2.34 (m, 1H, *cis*), 2.26 (m, 1H, C*H*, *trans*), 2.05 (s, 3H, Ac CH_3, *trans* and *cis*), 1.86 (m, 1H, *cis*), 1.49 (m, 1H, CH_2, *trans*), 1.31 (m, 1H, CH_2, *trans*), 1.18 (d, J = 7.5 Hz, 3H, CH_3, *trans*), 1.09 (d, J = 7 Hz, 3H, CH_3, *cis*), 1.04 (d, J = 6 Hz, 3H, CH_3, *cis*), 1.00 (d, J = 6 Hz, 3H, CH_3, *trans*), 0.8 (m, 1H, *cis*). ^{13}C{^{1}H} NMR (C_6D_6, 75 MHz): δ 177.8 (*C*O, *cis*), 177.1 (*C*O, *trans*), 169.5 (*C*O, *cis*), 169.3 (*C*O, *cis*), 53.5 (*cis*), 53.4 (*trans*), 35.9 (*cis*), 35.4 (*cis*), 34.2 (*trans*), 34.0 (*trans*), 21.1 (*trans*), 21.1 (*cis*), 19.5 (*cis*), 18.9 (*trans*), 16.7 (*trans*), 16.3 (*cis*). FTIR (thin film, cm^{-1}): 3449 (br), 3230 (br), 2974, 1707(s), 1669(s), 1531, 1453, 1417, 1374, 1262. GC-MS (EI, *m*/*z* (relative intensity)): 170(1) [M], 155(2), 128 (20), 113 (40), 99(3), 85(5), 69(8), 59(10), 43(12). ESI-MS (MeOH, *m*/*z*): 193 [M + Na]$^+$ (5), 209 [M + K]$^+$. HRMS (FAB): calcd for $C_{18}H_{15}N_2O_2$ [M + H]$^+$ *m*/*z* 171.11335, found *m*/*z* 171.11344.

***N*-Aminophthalimido-3,5-dimethylpyrrolidin-2-one (12b).** Reaction of **2b** (52 mg, 201 μmol) with Pt(bpy)Cl_2 (9 mg, 21 μmol) and AgOTf (11 mg, 43 μmol) in DMF (1.2 mL) followed by silica column chromatography with 3:2 Hex/EtOAc provided **12b** as a mixture of diastereomers (1:1 *cis*:*trans*), white solid (44.5 mg, 85%), mp 116 °C. ^{1}H NMR (C_6D_6, 500 MHz): δ 7.33 (m, 4H, Ar), 6.77 (m, 4H, Ar), 3.67 (m, 2H, NC*H*, *cis* and *trans*), 2.23 (m, 2H, C*H*, *cis* and *trans*), 1.73 (m, 1H, CH_2, *trans*), 1.40 (m, 2H, CH_2, *cis* and *trans*), 1.33 (m, 1H, CH_2, *cis*), 1.09 (d, J = 7.5 Hz, 3H, CH_3, *cis*), 1.02 (d, J = 7 Hz, 3H, CH_3, *trans*), 0.96 (d, J = 6.5 Hz, 6H, *cis* and *trans*). ^{13}C{^{1}H} NMR (C_6D_6, 75 MHz): δ 175.58 (*C*O), 165.66 (*C*O), Ar buried under solvent, 53.99, 53.69, 36.01, 35.29, 34.42, 33.62, 19.57, 16.66, 16.05. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 176.0, 165.4, 135.0, 134.9, 130.4, 130.3, 130.1, 130.0, 124.3, 124.1, 53.9, 53.7, 35.8, 35.1, 34.4, 33.7, 19.4, 16.0. FTIR (thin film, cm^{-1}): 1795, 1741 (s), 1720 (s), 1356, 1249, 1224, 1113, 1085, 882, 711. ESI-MS (MeOH, *m*/*z*): 163(10), 259 [M + H]$^+$ (1), 291 (3), 313 (10). HRMS (FAB): calcd for $C_{14}H_{15}N_2O_3$ [M + H]$^+$ *m*/*z* 259.10827, found *m*/*z* 259.10713.

***N*-Acetamido-4,5-dimethylpyrrolidinon-2-one (13a).** Reaction of **3a** (29 mg, 170 μmol) with Pt(bpy)Cl_2 (7 mg, 17 μmol) and AgOTf (10 mg, 39 μmol) in DMF (1.0 mL) followed by silica column chromatography with 10% MeOH in CH_2Cl_2 provided **13a** as a mixture of diastereomers (1:2.6 *cis*:*trans*), colorless oil (22 mg, 75%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.52 (s, 1H, N*H*, *cis*), 8.40 (s, 1H, N*H*, *trans*), 4.05 (m, 1H, NC*H*, *cis*), 3.58 (m, 1H, NC*H*, *trans*), 2.62 (m, 1H, C*H*, *cis*), 2.55 (m, J = 5 Hz, CH_2, 1H *trans*, 1H *cis*), 2.14 (m, 1H, CH_2, *trans*), 2.08 (m overlapping, 2H, CH_2, *cis*), 2.05 (s, 3H, AcCH_3, *cis* and *trans*), 1.98 (m, 1H, C*H*, *trans*), 1.20 (d, J = 3.6 Hz, 3H, CH_3, *trans*), 1.17 (d, J = 4.2 Hz, 3H, CH_3, *trans*), 1.08 (d, J = 4.2 Hz, 3H, CH_3, *cis*), 1.04 (d, J = 3.9 Hz, 3H, CH_3, *cis*). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 174.2 (*trans*), 173.7 (minor), 169.5 (*trans*), 169.4 (minor), 61.9 (*trans*), 58.2 (minor), 37.1(*trans*), 36.4 (*cis*), 34.7 (*trans*), 29.1 (*cis*), 21.1 (*trans*), 18.0 (*trans*), 17.6 (*trans*), 15.1 (*cis*), 13.1 (*cis*). GC-MS (EI, *m*/*z* (relative intensity)): 170(1) [M], 155(2), 128(50), 113(75), 112(45), 96(8), 85(5), 69(15), 59(30), 43(15).

***N*-Aminophthalimido-4,5-dimethylpyrrolidin-2-one (13b).** Reaction of **3b** (48 mg, 186 μmol) with Pt(bpy)Cl_2 (8 mg, 19 μmol) and AgOTf (10 mg, 39 μmol) in DMF (1.2 mL) followed by silica column chromatography with 3:2 hexanes/EtOAc provided **13b** as a mixture of diastereomers (1:6 *cis*:*trans*), white solid (30.6 mg, 64%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90 (m, 2H, Ar, *cis* and *trans*), 7.80 (m, 2H, Ar, *cis* and *trans*), 4.12 (m, 1H, C*H*, *cis*) 3.65 (m, 1H, C*H*, *trans*), 2.71 (m, 1H, C*H*, *cis* and *trans*), 2.24 (m, 2H, CH_2, *cis* and *trans*), 1.26 (d, J = 6 Hz, 3H, CH_3, *trans*), 1.24 (d, J = 6 Hz, 3H, CH_3, *trans*), 1.18 (d, J = 3.5 Hz, 3H, CH_3, *cis*), 1.17 (d, J = 3.5 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 172.8, 165.4, 165.1, 135.0, 134.9, 130.4, 130.4, 124.3, 124.1, 62.3 (*trans*), 58.6 (*cis*), 36.8 (*trans*), 36.4 (*cis*), 35.0 (*trans*), 30.1 (*cis*), 17.8 (*trans*), 17.7 (*trans*), 15.2 (*cis*), 13.8 (*cis*). ESI-MS (MeOH, *m*/*z*): 163(10), 259 (1) [M + H]$^+$, 291 (5), 313 (7). HRMS (FAB): calcd for $C_{14}H_{15}N_2O_3$ [M + H]$^+$ *m*/*z* 259.10827, found *m*/*z* 259.10721.

***N*-Acetamido-3,3,5-trimethylpyrrolidin-2-one (14a).** Reaction of **4a** (35 mg, 190 μmol) with Pt(bpy)Cl_2 (8 mg, 19 μmol) and AgOTf (10 mg, 39 μmol) in DMF (1.2 mL) for 2 days followed by silica column chromatography with 1% to 3% MeOH in CH_2Cl_2 gradient elution provided **14a** as a colorless oil (24.6 mg, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.53 (s, 1H, N*H*), 3.70 (m, 1H, C*H*), 1.84 (dd, J = 12.5, 6.5 Hz, 1H, CH_2), 1.78 (s, 3H, AcCH_3), 1.19 (dd, J = 12.5, 9 Hz, 1H, CH_2), 0.96 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.91 (d buried, 3H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 180.1 (*C*O), 169.5 (*C*O), 51.9, 42.2, 39.2, 25.6, 25.0 21.0, 19.4. FTIR (thin film, cm^{-1}): 3234 (br), 2964, 1720 (s), 1676, 1460, 1365, 1264. ESI-MS (MeOH, *m*/*z*): 143 [M + H − C_2O]$^+$ (4), 185 [M + H]$^+$ (5), 207 [M + Na]$^+$ (10), 223 [M + K]$^+$ (2). HRMS (FAB): calcd for $C_9H_{17}N_2O_2$ [M + H]$^+$ *m*/*z* 185.12900, found *m*/*z* 185.12877.

***N*-Aminophthalimido-3,3,5-trimethylpyrrolidin-2-one (14b).** Reaction of **4b** (137 mg, 503 μmol) with Pt(bpy)Cl_2 (21 mg, 50 μmol) and AgOTf (26 mg, 101 μmol) in DMF (3.2 mL) followed by silica column chromatography with 1:1 hexanes/EtOAc provided **14b** as a white solid (118 mg, 86%), mp 81 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92 (m, 2H, Ar), 7.81 (m, 2H, Ar), 4.06 (m, 1H, C*H*), 2.23 (t, J = 6 Hz, 1H, CH_2), 1.76 (m, 1H, CH_2), 1.35 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.27 (d, J = 6 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 178.6 (*C*O), 165.5 (*C*O), 165.2 (*C*O), 134.9 (Ar), 134.8 (Ar), 130.5 (Ar), 130.1 (Ar), 124.2 (Ar), 124.0 (Ar), 52.6, 42.4, 39.3, 25.3, 25.1, 19.4. FTIR (thin film, cm^{-1}): 1795, 1742 (s), 1467, 1384, 1354, 1256, 1214, 1116, 881, 710. GC-MS (EI, *m*/*z* (relative intensity)): 272(1) [M], 257 (10), 229(1), 202(1), 189(1), 162(12), 148(1), 132(2), 104(4), 83(25), 67(4), 55(8), 41(5). HRMS (FAB): calcd for $C_{15}H_{17}N_2O_3$ [M + H]$^+$ *m*/*z* 273.12388, found *m*/*z* 273.12274.

***N*-Acetamido-2-methylpiperidinone (15a).** Reaction of **5a** (31 mg, 182 μmol) with Pt(bpy)Cl_2 (8 mg, 19 μmol) and AgOTf (10 mg, 39 μmol) in DMF (1.1 mL) followed by silica column chromatography with 10% MeOH in CH_2Cl_2 afforded **15a** as a colorless oil (28 mg, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.86 (s, 1H, N*H*), 3.86 (sext, J = 4 Hz, 1H, C*H*), 2.49 (m, 1H, CH_2), 2.41 (m, 1H, CH_2), 2.07 (m, 1H, CH_2), 2.03 (s, 3H, AcCH_3), 1.82 (m, 1H, CH_2), 1.61 (m, 1H, CH_2), 1.21 (d, J = 4 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (CD_2Cl_2, 125 MHz) δ 170.5, 169.7, 56.2, 32.7, 30.8, 21.1, 19.8, 18.2. GC-MS (EI, *m*/*z* (relative intensity)): 170 (1) [M], 155(2), 128(50), 113(90), 99(20), 84(40), 55(25), 43(30). HRMS (FAB): calcd for $C_8H_{15}N_2O_2$ [M + H]$^+$ *m*/*z* 171.11335, found *m*/*z* 171.11336.

***N*-Acetamido-3,3,6-trimethylpiperidinone (16a).** Initial reaction of **6a** (29 mg, 146 μmol) with Pt(bpy)Cl_2 (7 mg, 16 μmol) and AgOTf (8 mg, 31 μmol) in DMF (1 mL) followed by silica column chromatography with 2% MeOH in CH_2Cl_2 yielded a mixture of **16a** and **6a** (20.6 mg, 70% yield with 8% **6a**), which was resubmitted to the reaction conditions to yield pure **16a** as a colorless oil after silica column chromatography with 5% MeOH in CH_2Cl_2 (20.1 mg, 69%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.54

(s, 1H, N*H*), 3.83 (m, 1H, C*H*), 2.09 (m, 1H, CH_2), 2.03 (s, 3H, AcCH_3), 1.69−1.57 (m, 3H, CH_2), 1.23−1.19 (m, 9H, 3CH_3). ^{13}C{^{1}H} NMR (CD_2Cl_2, 125 MHz): δ 176.7 (*C*O), 169.8 (*C*O), 56.6 (*C*H), 39.0, 32.9, 27.5, 29.0, 21.2, 20.0. FTIR (thin film, cm^{-1}): 3264, 2973, 2967, 1682 (s), 1638 (s), 1460, 1420, 1376, 1305, 1202, 1051. ESI-MS (MeOH, *m*/*z*): 157(2) [M + H − C_2O]$^+$ (2), 199 [M + H]$^+$ (4), 221 [M + Na]$^+$ (2), 237 [M + K]$^+$ (1). HRMS (FAB): calcd for $C_{10}H_{19}N_2O_2$ [M + H]$^+$ *m*/*z* 199.14465, found *m*/*z* 199.14465.

***N*-Phthalimido-3,3,6-trimethylpiperidinone (16b).** Reaction of **6b** (52 mg, 182 μmol) with Pt(bpy)Cl_2 (8 mg, 19 μmol) and AgOTf (10 mg, 39 μmol) in DMF (1.2 mL) followed by silica column chromatography with 2:1 Hex/EtOAc provided **16b** as a white solid (43 mg, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86 (m, 2H, Ar), 7.75 (m, 2H, Ar), 3.99 (m, 1H, C*H*), 2.10 (m, 1H, CH_2), 1.83 (m, 3H, CH_2), 1.32 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.25 (d, J = 6.6 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 175.2 (*C*O), 166.2 (*C*O phthal), 165.9 (*C*O phthal), 134.8 (Ar), 134.7 (Ar), 130.3 (Ar), 130.1 (Ar), 124.1 (Ar), 123.9 (Ar), 57.7, 39.2, 33.5, 27.6, 27.5, 27.3, 20.4. FTIR (thin film, cm^{-1}): 2974, 2936, 1975, 1737 (s), 1676, 1469, 1381, 1302, 1219, 1121, 1082, 883, 714. HRMS (FAB): calcd for $C_{16}H_{19}N_2O_3$ [M + H]$^+$ *m*/*z* 287.12957, found *m*/*z* 287.13936.

***N*-Acetamido-2-methylpyrrolidine (17a).** Reaction of **7a** (31 mg, 218 μmol) with Pt(bpy)Cl_2 (10 mg, 24 μmol) and AgOTf (12 mg, 47 μmol) in DMF (1.4 mL) followed by silica column chromatography with 2% MeOH in CH_2Cl_2 provided **17a** as a colorless oil (8 mg, 26%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.34 (s, 1H, N*H*), 4.02 (m, 1H, C*H*), 2.48−2.43 (m, 2H, CH_2), 2.31 (m, 2H, CH_2), 2.06 (s, 1H, AcCH_3), 1.74 (br m, 1H, CH_2), 1.66 (m, 1H, CH_2), 1.29 (d, J = 6.5 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (CD_2Cl_2, 125 MHz): δ 174.4 (*C*O), 169.4 (*C*O), 54.9, 28.5, 25.6, 21.1, 19.3. HRMS (FAB): calcd for $C_7H_{15}N_2O$ [M + H]$^+$ *m*/*z* 143.11844, found *m*/*z* 143.11842.

***N*-Benzamido-2-methylpyrrolidine (17c).** Reaction of **7c** (35 mg, 171 μmol) with Pt(bpy)Cl_2 (8 mg, 19 μmol) and AgOTf (10 mg, 39 μmol) in DMF (1.1 mL) followed by silica column chromatography with 1% MeOH in CH_2Cl_2 provided **17c** as a white solid (23.0 mg, 66%). The spectral data in DMSO-d_6 are consistent with published parameters.[13] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75 (d, J = 6.9 Hz, 2H, *o*), 7.43 (m, 3H, *m* and *p*), 6.69 (s br, 1H, N*H*), 3.44 (dt, J = 8.4, 2.7 Hz, 1H C*H*), 2.87(m, 1H, CH_2), 2.72 (q, J = 8.7 Hz, 1H, CH_2), 2.06−1.75 (m, 3H, CH_2), 1.60 (m, 1H, CH_2), 1.20 (d, J = 6.3 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (CD_2Cl_2, 125 MHz): δ 166.9 (*C*O), 134.2 (Ar), 131.7 (Ar), 128.8 (Ar), 127.2 (Ar), 62.4, 55.9, 30.4, 20.5, 18.4. ESI-MS (MeOH, *m*/*z*): 205 [M + H]$^+$ (20), 227 [M + Na]$^+$ (1). HRMS (FAB): calcd for $C_{12}H_{17}N_2O$ [M + H]$^+$ *m*/*z* 205.13409, found *m*/*z* 205.13375.

General Procedure for Synthesis of Pt Complexes. [Pt(bpy)(MeCN)$_2$](OTf)$_2$ was treated with the appropriate hydrazide in DMF and heated as described below. The Pt species was then precipitated with the addition of ether and filtered through glass wool, and the residue was extracted into DMF-d_7. Due to the noncrystalline nature of the complexes, elemental analyses are not available. ^{1}H NMR spectra for complexes **20**−**25** are included in the Supporting Information as an indication of purity. In all cases either the solution was decanted following precipitation or the mixture was filtered through glass wool and the solids were extracted into DMF-d_7, and in some cases CD_3CN, for spectroscopic analysis.

[(bpy)Pt(CH$_2$CH(CH$_2$)$_2$C(O)N-Nphthal)(CD$_3$CN)](OTf) (20). [Pt(bpy)(MeCN)$_2$](OTf)$_2$ (9.7 mg, 13 μmol) and **1b** (7.4 mg, 30 μmol) were combined in DMF-d_7 (400 μL). After heating at 80 °C for 5 h ∼88% conversion to **20** was observed by ^{1}H NMR analysis. Complex **20** was then purified according to the general procedure. ^{1}H NMR (CD_3CN, 500 MHz): δ 8.64 (d, J_{HH} = 10 Hz, J_{PtH} = 46.5 Hz, 1H, bpy), 8.31 to 8.01 (m, 6H, bpy), 7.65 (m, 1H, bpy), 7.53 to 7.42 (m, 4H, phthal Ar), 4.15 (m, 1H, C*H*), 2.54 to 2.41 (m, 2H, CH_2), 2.23 (m, 1H, Pt-CH_2), 1.88 (m, 2H, CH_2), 1.47 (dd, J_{HH} = 13.5, 19 Hz, J_{PtH} = 69 Hz Hz, 1H, Pt-CH_2). ^{19}F NMR (DMF-d_7, 282 MHz): δ −79.5. ESI-MS (CH_3CN, *m*/*z*): 594 [(bpy)Pt(CH$_2$CH(CH$_2$)$_2$C(O)N-Nphthal)]$^+$ (positive mode); 148 [OTf]$^-$ (negative mode).

[(bpy)Pt(CH$_2$CH(CH$_2$)$_2$C(O)N-N(CH$_3$)$_2$)](OTf) (21). [Pt(bpy)(MeCN)$_2$](OTf)$_2$ (24.0 mg, 32.8 μmol) and **1i** (24.0 mg, 169 μmol) were combined in DMF-d_7 (500 μL). After heating at 120 °C for 21 h ∼86% conversion to **21** was observed by ^{1}H NMR analysis. Complex **21** was then purified according to the general procedure. ^{1}H NMR (DMF-d_7, 300 MHz): δ 9.19 (d, J = 4.8 Hz, 1H, Ar), 8.98 (d, J = 5.7 Hz, 1H, Ar), 8.86 (d, J = 7.6 Hz, 1H, Ar), 8.78 (d, J = 8.1 Hz, 1H, Ar), 8.56 (t, J = 7.8 Hz, 1H, Ar), 8.53 (t, J = 7.5 Hz, 1H, Ar), 8.06 (t (overlapping with solvent), J = 6 Hz, 1H, Ar), 7.84 (t, J = 6 Hz, 1H, Ar), 4.34 (m, 1H, C*H*), 4.14 (s, J_{Pt-H} = 14.7 Hz, 3H, CH_3), 3.77 (s, J_{Pt-H} = 14.1 Hz, 3H, CH_3), 2.77 (m, 2H, CH_2), 2.47 (m, 1H, CH_2), 2.21 (m, 2H, Pt-CH_2), 1.69 (m, 1H, CH_2). ^{19}F NMR (DMF-d_7, 282 MHz): δ −79.6. ESI-MS (CH_3CN, *m*/*z*): 492 [M − OTf]$^+$ (positive mode); 148 [OTf]$^-$ (negative mode).

[(bpy)Pt(CH$_2$CH(CH$_2$)$_4$N-NHAc](OTf) (22). A mixture of hex-5-enyl-*N*′-acetyl hydrazide (32.0 mg, 205 μmol), Pt(bpy)Cl_2 (9.0 mg, 21 μmol), and AgOTf (11.0 mg, 21.4 μmol) was combined in DMF (1.2 mL). After heating at 120 °C for 24 h, the solvent was removed under vacuum, and the residue extracted into $CDCl_3$. Complete conversion to complex **22** was observed by ^{1}H NMR analysis. The solvent was removed under vacuum, the residue was extracted into DMF, and complex **22** was isolated as described in the general procedure. ^{1}H NMR (DMF-d_7, 300 MHz): δ 11.2 (s br, 1H, N*H*), 9.14 (d, J = 5.7 Hz, 1H, bpy), 9.00 (d, J = 5.7 Hz, 1H, bpy), 8.79 (t, J = 7.5 Hz, 2H, bpy), 8.53 (t, J = 7.5 Hz, 2H, bpy), 7.97 (obscured by solvent, 1H, bpy), 7.84 (t, J = 7.5 Hz, 1H, bpy), 4.12 (m, 1H, CH), 3.58 (m, 1H, CH$_2$), 3.28 (d, J = 11 Hz, 1H, CH$_2$), 2.81 (m obscured by solvent, 1H, CH$_2$), 2.45 (m, 1H, CH$_2$), 2.22 (s, 3H, CH_3), 2.18 (m, 2H, CH$_2$), 1.94 (m, 1H, CH$_2$), 1.79 (m, 1H, CH$_2$), 1.53 (m, 1H, CH$_2$). ESI-MS (CH_3CN, *m*/*z*): 506 [(bpy)Pt(CH$_2$CH(CH$_2$)$_4$N-NHAc]$^+$ (positive mode); 148 [OTf]$^-$ (negative mode).

[Pt(bpy)(κ^2-Me$_2$NN=C(O)(CH$_2$)$_2$CH=CH$_2$)](OTf) (23). [Pt(bpy)(MeCN)$_2$](OTf)$_2$ (20.0 mg, 27.3 μmol) and **1i** (15.0 mg, 105 μmol) were combined in DMF-d_7 (0.5 mL), and the mixture was allowed to react at RT. After 1.5 h, complete conversion to **23** was observed by ^{1}H NMR analysis, and complex **23** was then precipitated with ether and isolated as described in the general procedure. ^{1}H NMR (DMF-d_7, 300 MHz): δ 9.15 (t, J = 5.7 Hz, 2H, bpy), 8.84 (dd, J = 3, 7.5 Hz, 2H, bpy), 8.62 (t, J = 6 Hz, 2H, bpy), 8.02 (quin, J = 7 Hz, 2H, bpy), 5.92 (m, 1H, =C*H*), 5.05 (dd, J = 17.5, 10.2 Hz, 2H, =CH_2), 3.32 (s, J_{PtH} = 11 Hz, 6H, CH_3), 2.48 (m, 4H, CH_2). ESI-MS (CH_3CN, *m*/*z*): 492 [Pt(bpy)(η^2-Me$_2$NN=C(O)(CH$_2$)$_2$CH=CH$_2$)]$^+$ (positive mode); 148 [OTf]$^-$ (negative mode).

[Pt$_2$bpy$_2$(AcNNAc)](OTf)$_2$ (24). [Pt(bpy)(MeCN)$_2$](OTf)$_2$ (10 mg, 14 μmol) and AcNHNHAc (5 mg, 43 μmol) were combined in DMF-d_7. After heating at 120 °C for 18 h ∼90% conversion to 24 was observed by ^{1}H NMR analysis. Complex **24** was then isolated as described in the general procedure. ^{1}H NMR (DMF-d_7, 500 MHz): δ 9.36 (d, J = 5.5 Hz, 1H, bpy N=CH), 9.00 (d, J = 5.5 Hz, 1H, bpy N=CH), 8.86 (d, J = 8.5 Hz, 1H, bpy), 8.82 (d, J = 8 Hz, 1H, bpy), 8.68 (t, J = 7 Hz, 1H, bpy), 8.62 (t, J = 8 Hz, 1H, bpy), 8.09 (t, J = 6.5 Hz, 1H, bpy), 7.96 (t, J = 6 Hz, 1H, bpy), 2.76 (s, 3H, CH_3). ESI-MS (CH_3CN, *m*/*z*): 965 [Pt$_2$bpy$_2$(AcNNAc)(OTf)]$^+$, 408 [Pt$_2$bpy$_2$(AcNNAc)]$^{2+}$ (positive mode); 148 [OTf]$^-$ (negative mode).

[(bpy)$_2$Pt$_2$(AcNNC(O)(CH$_2$)$_2$CH=CH$_2$)](OTf)$_2$ (25). Pt(bpy)Cl_2 (14.6 mg, 34.6 μmol), AgOTf (20 mg, 78 μmol), and **1a** (11.5 mg, 73.7 μmol) were combined in DMF-d_7 (0.5 mL), and the mixture was allowed to react at RT. After 22 h, >95% conversion to **25** was observed by ^{1}H NMR analysis. Complex **25** was then isolated as described in the general procedure. Attempts to isolate Pt complex **25** on larger scales (50−100 mg Pt(bpy)Cl_2) by filtration

through an air-free frit were unsuccessful due to formation of gooey material, which clogged the frit. ^{1}H NMR (DMF-d_7, 300 MHz): δ 9.39 (d, J = 5.7 Hz, 1H, bpy N=C*H*), 9.30 (d, J = 5.7 Hz, 1H, bpy), 9.16 (d, J = 5.7 Hz, 1H, bpy), 9.04 (d, J = 5.7 Hz, 1H, bpy), 8.88 (m, 4H, bpy), 8.67 (m, 4H, bpy), 8.11 (t, J = 6 Hz, 2H, bpy), 7.94 (m, 2H, bpy), 5.92 (m, 1H, =C*H*), 5.04 (dd, J = 16.2, 10.2 Hz, 2H, =CH_2), 3.15 (t, J = 7.2 Hz, 2H, CH_2), 2.74 (m beneath solv, 5H, 2CH_2 and 3CH_3). ^{19}F NMR (DMF-d_7, 282 MHz): δ −79.1. ESI-MS (CH_3CN, m/z): 1007 $[(bpy)_2Pt_2(AcNNC(O)(CH_2)_2CH{=}CH_2)(OTf)]^+$, 428 $[(bpy)_2Pt_2(AcNNC(O)(CH_2)_2CH{=}CH_2)]^{2+}$ (positive mode); 148 $[OTf]^-$ (negative mode).

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Supporting Information Available: The CIF for compound **23**, full experimental details, characterization data for all new compounds, descriptions of stereochemical assignments, and kinetic data. This information is available free of charge via the Internet at http://pubs.acs.org.

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