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Mechanism of the Platinum(II)-Catalyzed Hydroamination of 4-Pentenylamines

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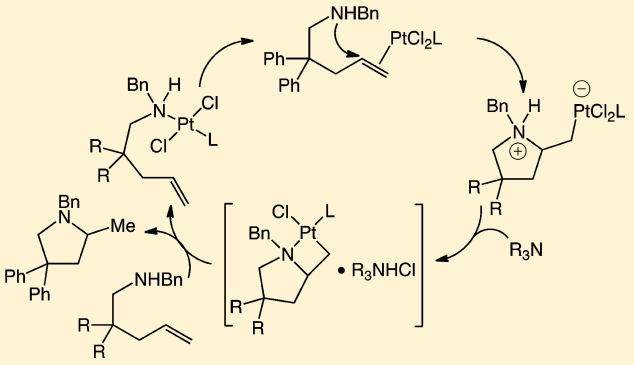
Supporting Information

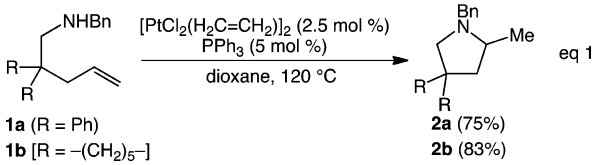
ABSTRACT: The mechanism of the platinum(II)-catalyzed intramolecular hydroamination of benzyl 4-pentenylamines has been evaluated under stoichiometric and catalytic conditions. Reaction of a benzyl 2,2-disubstituted 4-pentenylamine with $[(PPh_3)Pt(\mu\text{-}Cl)Cl]_2$ forms a thermally sensitive platinum amine complex that undergoes irreversible, intramolecular ligand exchange with the pendant C═C bond to form a reactive platinum π-alkene complex. The π-alkene complex undergoes rapid, outer-sphere C−N bond formation, evidenced by the anti addition of Pt and N across the complexed C═C bond, to form a thermally stable zwitterionic platinamethylpyrrolidinium complex. The zwitterionic complex is rapidly and exergonically deprotonated by free amine to form a neutral, bicyclic azaplatinacyclobutane complex that likely exists as a discrete 1:1 adduct with ammonium salt in the nonpolar reaction medium and that represents the resting state of the catalytic cycle. Turnover-limiting intramolecular protodemetalation of the azaplatinacyclobutane−ammonium adduct followed by ligand exchange releases the 2-methylpyrrolidine product.



INTRODUCTION

The catalytic addition of the N−H bond of an amine across a C−C multiple bond has attracted considerable attention as a potentially expedient and atom-economical route to the synthesis of acyclic amines and nitrogen heterocycles.[1] Of the myriad permutations of catalytic hydroamination, the addition of the N−H bond of an unprotected alkylamine across an unactivated C═C bond represents one of the most challenging and synthetically desirable variants, and most of the progress in this area has been realized in the context of the intramolecular hydroamination of amino alkenes.[2] Although the intramolecular hydroamination of amino alkenes is catalyzed efficiently by rare earth,[3] alkaline earth,[4] and group 4[5] metal complexes, the synthetic utility of these methods is compromised by the poor functional group compatibility and high air and moisture sensitivity of the catalysts. Brønsted acids also catalyze the intramolecular hydroamination of amino alkenes, albeit under forcing conditions.[6]

Owing to the limitations associated with early transition metal or Brønsted acid catalyzed hydroamination of amino alkenes, there has been considerable interest in the development of late transition metal catalysts for the intramolecular hydroamination of alkenes with alkylamines.[1] The first headway toward this objective was made by Bender and Widenhoefer, who described the intramolecular hydroamination of γ- and δ-alkenylamines catalyzed by a 1:2 mixture of Zeise's dimer and PPh_3 (eq 1).[7,8] Since this time, effective methods for the intramolecular hydroamination of amino alkenes catalyzed by Rh(I),[9−14] Ir(I),[14−16]



Cu(II),[17] Zn(II),[18,19] Pt-NHC,[20] and Pt(II) *o*-biphenylphosphine complexes have been disclosed.[21]

Experimental investigations of alkene hydroamination catalyzed by late transition metal complexes have established mechanisms involving either alkene insertion into the M−N bond of a metal amido complex (inner sphere) or addition of the nucleophile to the coordinated C═C bond of a metal alkene complex (outer sphere).[10,11,15,16,19,22−26] However, only a small subset of these mechanistic investigations involves the hydroamination of nonconjugated, electronically unactivated alkenes with alkylamines and, of these,[10,11,15,16,19] most lack the direct observation of catalytically relevant intermediates and/or information regarding the stereochemistry of C−N bond formation. A notable exception is Hartwig's investigation of intramolecular hydroamination of primary and secondary 4-pentenyl amines catalyzed by a rhodium mono(phosphine) complex, which established rhodium π-alkene resting states that were consumed via rapid and reversible outer-sphere C−N bond formation followed by turnover-limiting protodemetalation.[10,11]

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Although the reactions of alkylamines with platinum π-alkene complexes have been investigated,[27−40] the systems under investigation were not competent hydroamination catalysts. Rather, extant studies of platinum-catalyzed alkene hydroamination are restricted to transformations employing less basic nitrogen nucleophiles. Mayer and Michael have investigated the mechanism of the platinum-catalyzed intramolecular hydrohydrazination of alkenes and proposed a pathway involving inner-sphere C−N bond formation, although there was no direct experimental information to support this contention.[41] Tilley has studied the mechanism of the intermolecular hydroamination of norbornene with sulfonamides catalyzed by electron-deficient platinum bis(triflate) complexes and identified a Brønsted acid catalyzed pathway involving protonation of norbornene with a platinum−sulfonamide complex.[42] Poli has investigated the intermolecular hydroamination of ethylene with aniline catalyzed by $PtBr_2$ both experimentally and computationally and has proposed mechanisms involving outer-sphere addition of aniline on a platinum ethylene complex.[43]

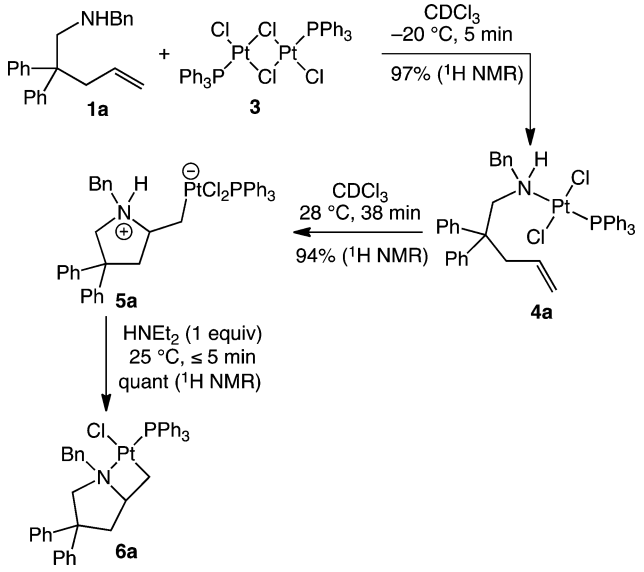
Herein we report the mechanistic analysis of the platinum-catalyzed intramolecular hydroamination of the benzyl 2,2-disubstituted 4-pentenylamines **1** to form pyrrolidines **2** (eq 1).[44] This study includes the synthesis and evaluation of potential intermediates, stereochemical analysis of C−N bond formation, identification of the catalyst resting state and turnover-limiting step, and kinetic and spectroscopic analysis of catalytically active mixtures. These data support a mechanism involving outer-sphere C−N bond formation and turnover-limiting protodemetalation of a bicyclic azaplatinacyclobutane complex.

RESULTS AND DISCUSSION

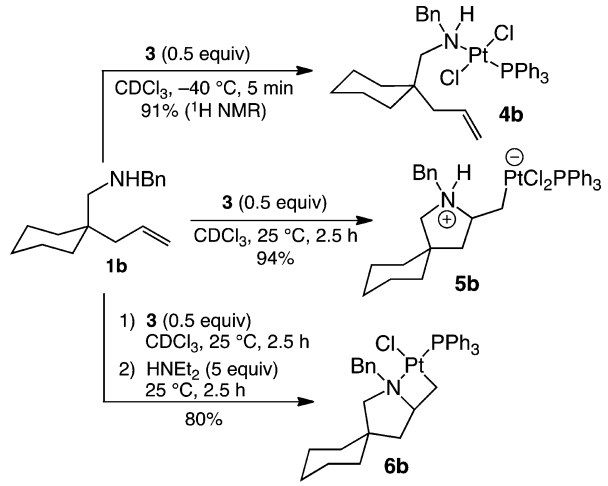
Synthesis of N-Bound Platinum 4-Pentenylamine Complexes 4. To gain insight into the mechanism of the platinum(II)-catalyzed intramolecular hydroamination of 4-pentenylamines **1**, we analyzed the stoichiometric reactions of **1** with the chloride-bridged phosphine dimer $[(PPh_3)Pt(\mu\text{-}Cl)Cl]_2$ (**3**). Alkene-free dimer **3**,[45] which is also an active hydroamination catalyst, was employed in preference to Zeise's dimer to avoid possible complications associated with ethylene displacement. To this end, treatment of benzyl 2,2-diphenyl-4-pentenylamine (**1a**; 15 mM) with **3** (0.5 equiv) in $CDCl_3$ at −20 °C led to immediate (≤5 min) bridge cleavage and formation of the mononuclear platinum amine complex $(PPh_3)Pt\{\kappa^1\text{-}N\text{-}[NH(Bn)CH_2C(Ph)_2CH_2CH{=}CH_2]\}Cl_2$ (**4a**) in 97% yield (^{1}H NMR; Scheme 1). In a similar manner, reaction of cyclohexyl-substituted 4-pentenylamine **1b** (15 mM) with **3** (0.5 equiv) in $CDCl_3$ at −40 °C for 5 min led to formation of the platinum amine complex $(PPh_3)Pt\{\kappa^1\text{-}N\text{-}[NH(Bn)CH_2C\text{-}[-(CH_2)_5-]CH_2CH{=}CH_2]\}Cl_2$ (**4b**) in 91% yield (^{1}H NMR; Scheme 2).

Complexes **4** were thermally unstable and were characterized without isolation by NMR spectroscopy. For example, complexation of the nitrogen atom of **4a** to platinum was established by the large downfield shift of the amine proton of **4a** (δ 3.81) relative to that of free **1** (δ 0.90), by the presence of diastereotopic benzylic (δ 4.52, 3.44), C1 (δ 4.13, 3.15), and C3 (δ 4.57, 3.15) protons of the 4-pentenyl ligand of **4a**, and by the presence of residual ^{31}P−^{1}H coupling observed for one of the diastereotopic C1 methylene protons (δ 4.57 (J_{PH} = 8.0 Hz)). Although the ^{1}H NMR resonance of the internal olefinic proton of **4a** (δ 5.94) was shifted downfield relative to that of free **1** (δ 5.33), olefin coordination in **4a** was firmly discounted due to the absence of ^{195}Pt satellites for the olefinic resonances and by

Scheme 1



Scheme 2



the similar chemical shifts and one-bond C=C coupling constant of the olefinic carbon atoms of the ^{13}C-labeled isotopomer $(PPh_3)Pt\{\kappa^1\text{-}N\text{-}[NH(Bn)CH_2C(Ph)_2{}^{13}CH_2{}^{13}CH{=}{}^{13}CH_2]\}Cl_2$ (**4a**-$^{13}C_3$) (δ 131.5, 120.6, ($^1J_{C=C}$ = 69 Hz)) relative to those of **1a**-3,4,5-$^{13}C_3$ (δ 135.0, 117.7 ($^1J_{C=C}$ = 69 Hz)). The trans arrangement of the phosphine and amine ligands of **4a** was unambiguously established by the large ^{31}P−^{15}N coupling constant (J_{PN} = 47 Hz) in the ^{31}P{^{1}H} NMR spectrum of the ^{15}N isotopomer $(PPh_3)Pt\{\kappa^1\text{-}N\text{-}[^{15}NH(Bn)CH_2C(Ph)_2CH_2CH{=}CH_2]\}Cl_2$ (**4a**-^{15}N).[46]

Synthesis of Zwitterionic Platinamethylpyrrolidinium Complexes 5. When were warmed to room temperature, N-bound 4-pentenylamine complexes **4** underwent rearrangement and cyclization to form the thermally stable zwitterionic platinamethylpyrrolidinium complexes **5** (Schemes 1 and 2). For example, warming a $CDCl_3$ solution of **4a** (29 mM) at 28 °C for 1 h formed $(PPh_3)Pt[CH_2CHNH(Bn)CH_2CPh_2CH_2]Cl_2$ (**5a**) in 94% yield without formation of detectable intermediates (^{1}H NMR, Scheme 1). Complex **5a** was isolated in quantitative yield from the corresponding preparative-scale reaction of **1a** and **3**. In a similar manner, the cyclohexyl-substituted

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platinamethylpyrrolidinium complex **5b** was isolated in 94% yield from the reaction of **1b** and **3** at 25 °C (Scheme 2).

Complexes **5** were fully characterized by NMR spectroscopy and mass spectrometry. For example, formal insertion of the C═C bond into the Pt−N bond of **4a** was established by the absence of olefinic resonances in the ^{1}H and ^{13}C NMR spectra of **5a** and its ^{13}C-labeled isotopomer $(PPh_3)Pt[^{13}CH_2{}^{13}CHNH(Bn)CH_2CPh_2{}^{13}CH_2]Cl_2$ (**5a**-$^{13}C_3$) and by the presence of diastereotopic protons at δ 1.94 and 1.42 that displayed partially resolved ^{1}H−^{195}Pt satellites in the ^{1}H NMR spectrum of **5a** assigned to the platinum-bound methylene protons. The presence of a cationic nitrogen atom in **5a** was established by the large downfield shift of the ammonium proton of **5a** (δ 10.1), identified by D_2O exchange, relative to the amine proton of **4a** (δ 3.81).

Synthesis of Bicyclic Azaplatinacyclobutane Complexes 6. Zwitterionic complexes **5** reacted rapidly and exergonically with free amine to form neutral, thermally stable azaplatinacyclobutane complexes **6** (Schemes 1 and 2). For example, treatment of **5a** (33 mM) with diethylamine (1 equiv) in $CDCl_3$ at room temperature for 5 min formed $(PPh_3)Pt\{\kappa^2$-C,N-$[CH_2CHN(Bn)CH_2CPh_2CH_2]Cl$ (**6a**) in quantitative yield by ^{1}H NMR spectroscopy (Scheme 1). In a separate experiment, when a CD_2Cl_2 solution of **5a** (30 mM) was treated with diethylamine (1.05 equiv) at −90 °C and monitored periodically by ^{1}H NMR spectroscopy, conversion of **5a** to **6a** was complete within 5 min without detectable formation of any intermediates. In a preparative-scale experiment, a solution of **1a** and **3** (0.5 equiv) was stirred at room temperature overnight and then treated with diethylamine. Aqueous workup and crystallization from chloroform/pentane at −10 °C gave **6a** in 64% yield as a white solid. In a similar manner, the cyclohexyl-substituted azaplatinacyclobutane **6b** was isolated in 80% yield as a pale yellow solid from the reaction of **1b** and **3** followed by treatment with diethylamine (Scheme 2).

Complexes **6** were fully characterized in solution and, in the case of **6a**, by X-ray crystallography. In particular, formation of the azaplatinacyclobutane ring was established by the presence of phosphorus−nitrogen coupling in the ^{31}P{^{1}H} NMR spectrum ($^{3}J_{NP}$ = 47.4 Hz) of the ^{15}N-labeled isotopomer $(PPh_3)Pt\{\kappa^2$-C,N-$[CH_2CH^{15}N(Bn)CH_2CPh_2CH_2]Cl$ (**6a**-^{15}N), consistent with a trans arrangement of the amine and phosphine ligands.[46] Worth noting in the ^{1}H NMR spectrum of **6a** were the diastereotopic platinum-bound methylene protons at δ 0.06 (H_{trans}) and δ −0.34 (H_{cis}), which displayed well-resolved ^{1}H−^{195}Pt satellites ($J_{PtH} \approx 100$ Hz) and which were unambiguously assigned by 2D ^{1}H−^{1}H NOESY/COSY analysis (Figure 1). These assignments were key to determination of the stereochemistry of C−N bond formation (see below).

Slow evaporation of a CH_2Cl_2 solution of **6a** gave crystals of the solvate complex **6a**·$^{1}/_{2}CH_2Cl_2$ suitable for single-crystal X-ray diffraction analysis. In the solid state, **6a** displayed a distorted-square-planar arrangement with an acute N−Pt−C(1) angle (70°) and expanded N−Pt−Cl (~94°), Cl−Pt−P (96°), and P−Pt−C(1) (100°) angles (Figure 2). The azaplatinacyclobutane moiety deviates slightly from planarity with a C(1)−Pt−N-C(2) dihedral angle of 6.6° with a narrow C(1)−Pt−N angle of 70° and a wide C(1)−C(2)−N angle of 103.3°. The Pt−Cl bond is long (2.41 Å) but is typical for a Pt−Cl bond trans to a strong σ-donor alkyl ligand.[47] The bond lengths and angles of **6a** are similar to those of the related monocyclic azaplatinacyclobutane

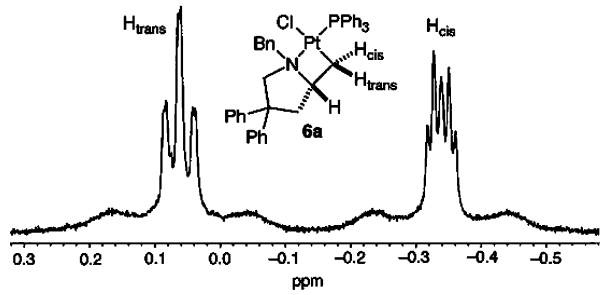

Figure 1. Partial ^{1}H{^{31}P} NMR spectrum of **6a** showing the Pt-bound methylene proton resonances.

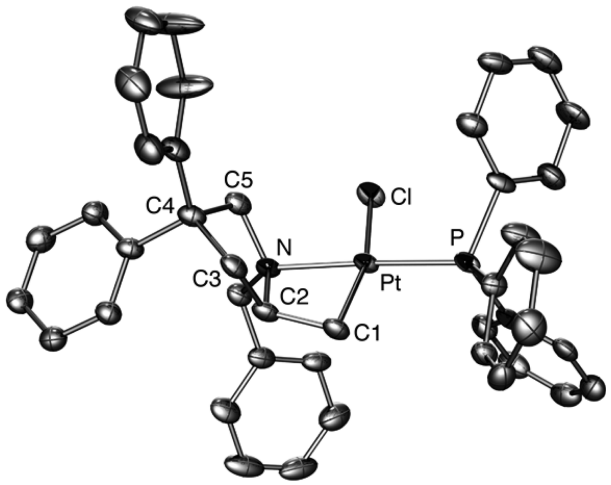

Figure 2. ORTEP diagram of **6a**·$^{1}/_{2}CH_2Cl_2$. Ellipsoids are shown at the 50% probability level with hydrogen atoms and solvent omitted for clarity. Selected bond lengths (Å) and angles (deg) for **6a**: Pt−Cl = 2.4097(13), Pt−P = 2.2049(14), Pt−C1 = 2.039(5), Pt−N = 2.121(4), C1−C2 = 1.533(4), C2−N = 1.514(4); N−Pt−C(1) = 70.08(15), C(1)−Pt−P = 100.02(13), N−Pt−P = 168.7(1), C(1)−Pt−Cl = 163.96(13), N−Pt−Cl = 94.44(10), P−Pt−Cl = 95.77(5), C(1)−C(2)−N = 103.3(4), C(2)−N−Pt(1) = 91.5(3), C(2)−C(1)−Pt = 94.1(3), C(1)−C(2)−C(3) = 114.5(4), C(1)−Pt−N−C(2) = 6.6.

complex $(PPh_3)Pt[\kappa^2$-C,N-$(CH_2CH_2NMe_2)]Cl$ (**7**),[48] despite the presence of the fused pyrrolidine ring in **6a**.

Treatment of **6b** with a 10-fold excess of $HNEt_3Cl$ in dioxane-d_8/diglyme (15/85) or excess HCl in $CDCl_3$ at −50 °C led to no detectable regeneration of **5b** before the onset of protodemetalation, pointing to the highly exergonic formation of azaplatinacyclobutanes **6** from **5** and free amine (see below).

Reactions of Amines with Platinum Alkene Complexes. The reactions of amines with platinum π-alkene complexes to form β-ammonioethanide, and in some cases azaplatinacyclobutane, complexes have been investigated for over 40 years, although never in the context of an intramolecular C−N bond forming event.[27−40] The reaction of a nitrogen nucleophile with a platinum(II) π-alkene complex to form a zwitterionic β-ammonioethanide complex was first reported in 1968 by Orchin, who demonstrated the reversible formation of $PtCl_2(Py)(CH_2CH_2Py)$ via reaction of pyridine with platinum ethylene complex $PtCl_2(pyridine)(\pi$-$H_2C{=}CH_2)$.[28] Panunzi and coworkers investigated the stoichiometric reactions of alkylamines with Pt(II) diene[29] and monoolefin complexes[30] and established the anti stereochemistry and outer-sphere nature of C−N bond formation.[31] Green likewise investigated the energetics of the reversible conversion of the platinum ethylene complexes

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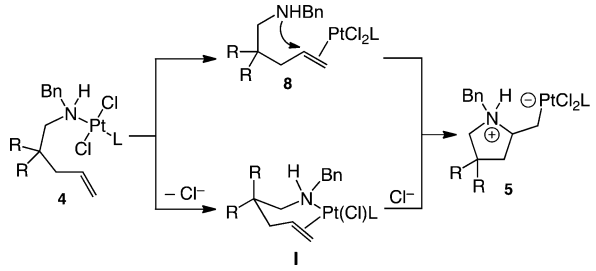
$PtCl_2(amine)(\pi\text{-}H_2C{=}CH_2)$ and amine to β-ammonioethanide complexes $PtCl_2(amine)(\sigma\text{-}H_2CCH_2NR_3)$ as a function of amine and found that K_{eq} increased with decreasing steric bulk and increasing basicity of the amine. As a benchmark, thermodynamic parameters of $\Delta H = -7.4$ kcal mol^{-1} and $\Delta S = -20$ eu were determined for amine = Et_2NH.[32] More recently, Atwood has demonstrated that addition of diethylamine to $(PPh_3)PtCl_2(\pi\text{-alkene})$ (alkene = propene, 1-butene) at low temperature forms predominantly the anti-Markovnikov product, which rearranges to the Markovnikov product at room temperature.[33] Similar observations were made by Maresca for addition of amines to a cationic tetramethylenediamine platinum alkene complex.[34] Panunzi also showed that the Pt−C bond of the zwitterionic β-ammonioethanide complex undergoes proto-demetalation with concentrated aqueous HCl to release the ethylated ammonium salt.[30]

Platinum Azaplatinacyclobutane Complexes. The conversion of a zwitterionic platinum β-ammonioethanide complex to an azaplatinacyclobutane complex was first documented by Green in 1979, who reported that the reaction of $(PPh_3)PtCl_2(\pi\text{-}H_2C{=}CH_2)$ with excess dimethylamine generated the neutral azaplatinacyclobutane complex $(PPh_3)PtCl[\kappa^2\text{-}C,N\text{-}(CH_2CH_2NMe_2)]$ (**7**).[35] Since that time, several azaplatinacyclobutene complexes, including **7**, have been structurally characterized.[34−37,48] Further investigation by Green and others revealed that conversion of the zwitterionic platinum β-ammonioethanide complex to the azaplatinacyclobutane complex is facilitated by alkyl substitution on the amine nitrogen atom and/or alkene sp^2 carbon atoms and by trans-labilizing ligands such as triphenylphosphine.[38−40] Green found that the equilibrium constants for the formation of azaplatinacyclobutanes from the reaction of $(PPh_3)PtCl_2(\pi\text{-}H_2C{=}CH_2)$ with excess secondary amine were too large to measure accurately and were on the order of $K = 1 \times 10^6$ M^2.[39] Importantly, Green also found that the ammonium salt generated in the conversion of $(PPh_3)PtCl_2(\pi\text{-}H_2C{=}CH_2)$ to **7** remained intimately associated with the azaplatinacyclobutane complex in the form of the isolable 1:1 adduct **7**·Me_2NH_2Cl,[39] although the nature of this interaction was not clarified. Washing the 1:1 adduct with water and methanol produced the neutral azaplatinacyclobutane **7** that, aside from the absence of resonances associated with the ammonium salt, was spectroscopically indistinguishable from **7**·Me_2NH_2Cl.[35,39,40] The formation of 1:1 azaplatinacyclobutane−ammonium ion adducts in nonpolar solvents has important implications on the kinetics of Pt(II)-catalyzed hydroamination (see below).

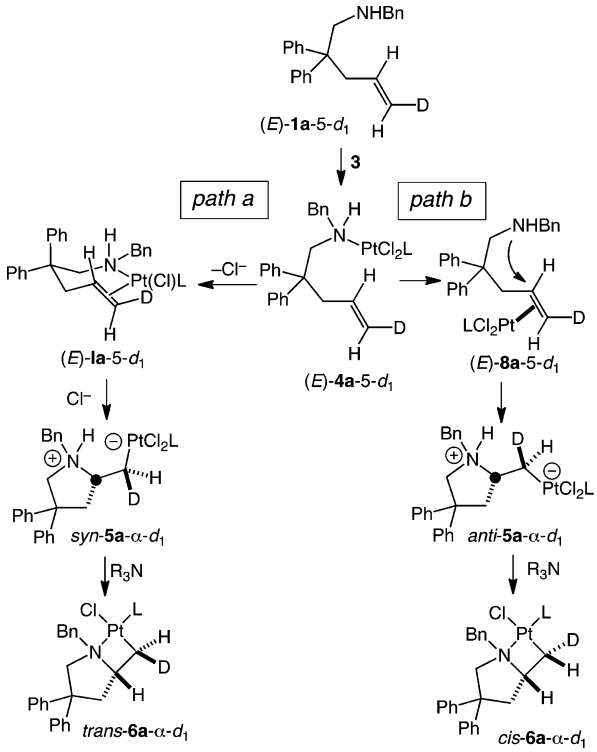
Stereochemistry of the Conversion of 4 to 5. Owing to the precedent for outer-sphere intermolecular addition of nucleophiles to platinum(II) π-alkene complexes,[31] we envisioned a mechanism for the conversion of **4** to **5** involving associative ligand exchange to form the platinum π-alkene complex **8** followed by intramolecular outer-sphere attack of the pendant amine on the complexed C=C bond. Alternatively, C−N bond formation could occur through an inner-sphere pathway involving, for example, chloride displacement to generate platinum amino alkene complex **I** followed by β-migratory insertion and chloride addition (Scheme 3).

Our approach to distinguish between inner- and outer-sphere pathways for the conversion of **4** to **5** involved the stereochemical analysis of the stoichiometric reaction of **3** with stereochemically pure, deuterium-labeled amino alkenes (*E*)- and (*Z*)-**1a**-5-*d* (Scheme 4). For example, in the inner-sphere pathway, β-migratory insertion of the coordinated alkene into the Pt−N

Scheme 3



Scheme 4



bond of platinum amino alkene complex (*E*)-**1a**-5-*d* would form *syn*-**5a**-*α*-*d* with net syn addition of nitrogen and platinum across the C=C bond of the alkene (Scheme 4, path a). Conversely, in the outer-sphere pathway, nucleophilic addition of the amine to the coordinated C=C bond of the π-alkene complex (*E*)-**8a**-5-*d* would yield *anti*-**5a**-*α*-*d* with net anti addition of the nitrogen and platinum across the C=C bond of the alkene (Scheme 4, path b). Although there is no obvious way that the diastereomeric, zwitterionic isotopomers *syn*-**5a**-*α*-*d* and *anti*-**5a**-*α*-*d* could be distinguished spectroscopically, the corresponding azaplatinacyclobutane isotopomers *cis*-**6a**-*α*-*d* and *trans*-**6a**-*α*-*d* formed via base-mediated cyclization of *syn*-**5a**-*α*-*d* and *anti*-**5a**-*α*-*d*, respectively, are readily distinguished by ^{1}H NMR spectroscopy (Figure 1).

In one experiment, treatment of (*E*)-**1a**-5-*d* with **3** (0.6 equiv) in $CDCl_3$ at room temperature for 2 h followed by addition of diethylamine (1.0 equiv) formed *cis*-**6a**-*α*-*d* as the exclusive stereoisomer with ≥95% isotopic purity by ^{1}H NMR analysis (eq 2). In a second experiment, treatment of a $CDCl_3$ solution of (*Z*)-**1a**-5-*d* with **3** led to formation of *trans*-**6**-*α*-*d* as the exclusive stereoisomer with ≥95% isotopic purity by ^{1}H NMR analysis (eq 3). These results establish the net anti addition of N and Pt across the olefinic C=C bond of **1a** and provide strong support

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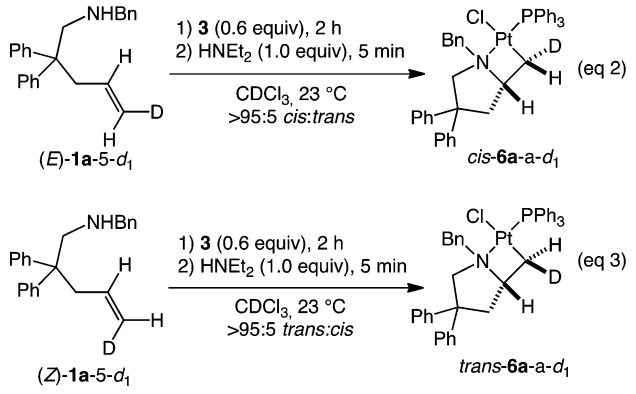


for an outer-sphere pathway for C−N bond formation in the platinum-catalyzed conversion of **1** to **2** (Scheme 4, path b).

Kinetics of the Conversion of 4 to 5. Although no intermediates were observed by NMR spectroscopy in the conversion of **4a** to **5a**, stereochemical analysis of the cyclization of isotopically labeled alkenyl amines (*E*)- and (*Z*)-**1a**-5-*d* directly implicated the platinum alkene complex **8a** in the conversion of **4a** to **5a**. To further delineate the mechanism of the conversion of **4a** to **5a**, we analyzed the kinetics of this transformation in $CDCl_3$ at 28 °C employing ^1H NMR analysis (Table S1 in the Supporting Information). A plot of ln[**4a**] versus time was linear to >3 half-lives, with a first-order rate constant of $k_{obs} = (1.66 \pm 0.02) \times 10^{-3}$ s^{-1} ($\Delta G^{\ddagger}_{301\,K} = 21.45 \pm 0.01$ kcal mol^{-1}, Figure 3). First-order rate constants for the

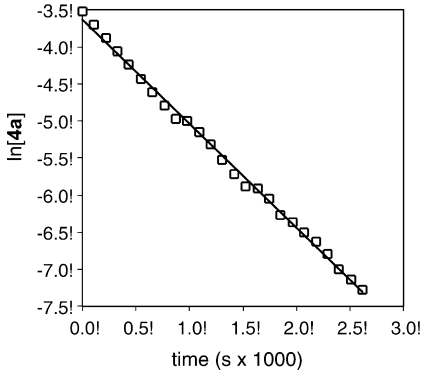


Figure 3. First-order plot of the conversion of **4a** (29 mM) to **5a** in $CDCl_3$ at 28 °C.

conversion of **4a** to **5a** were likewise obtained as a function of temperature from 7 to 40 °C. Eyring analysis of this data provided the activation parameters for the conversion of **4a** to **5a**: $\Delta H^{\ddagger} = 13.0 \pm 0.7$ kcal mol^{-1} and $\Delta S^{\ddagger} = -28 \pm 1$ eu (Figure 4).

The first-order rate law and activation parameters for the conversion of **4a** to **5a** are consistent with conversion of **4a** to **5a** through a highly ordered transition state, and the following two kinetic scenarios are consistent with these observations: (1) rapid, endergonic ligand exchange to form **8a** followed by rate-limiting C−N bond formation or (2) rate-limiting, irreversible ligand exchange to form **8a** followed by rapid C−N bond formation (Scheme 5). Our approach to distinguish these two possibilities involved independent generation of platinum alkene complex **8a** under conditions for which the conversion of **4a** to **5a** is slow. Under such conditions, if the conversion of **4a** to **5a** were to occur via scenario 1, in situ generation of **8a** would

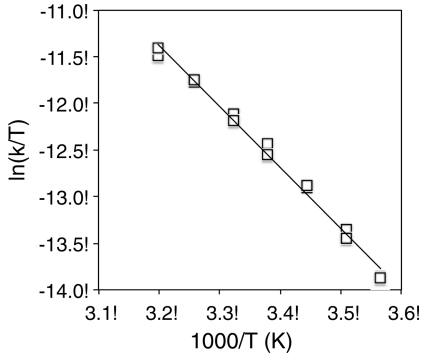
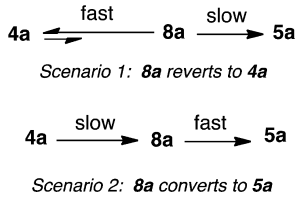


Figure 4. Eyring plot for the conversion of **4a** (~30 mM) to **5a** in $CDCl_3$ over the temperature range 7−40 °C.

Scheme 5



lead to rapid reversion to form platinum amine complex **4a**. Alternatively, if conversion of **4a** to **5a** were to occur via scenario 2, in situ generation of **8a** would lead to rapid cyclization to form zwitterion **5a** (Scheme 5).

Toward the independent generation of platinum π-alkene complex **8a**, we targeted the platinum π-4-pentenylammonium precursor **8a**·HBF_4, which could be deprotonated to reveal **8a** under conditions for which the conversion of **4a** to **5a** is slow. Preliminary experiments directed toward the synthesis of **8a**·HBF_4 revealed both that Zeise's dimer was an unsuitable precursor for the synthesis of **8**·HBF_4 owing to the high binding affinity of ethylene to Pt(II) and that ^1H NMR spectroscopy was unsuitable for the characterization of **8a**·HBF_4 owing to excessive broadening of the key vinylic resonances in the ^1H NMR spectrum, presumably due to fluxional behavior and/or hydrogen bonding. To avoid these complications, we targeted the ^{13}C-labeled isotopomer **8a**-3,4,5-$^{13}C_3$·HBF_4, which was generated via reaction of the ^{13}C-labeled 4-pentenyl ammonium salt **1a**-3,4,5-$^{13}C_3$·HBF_4 with the platinum propene precursor *cis*-$(PPh_3)Pt(\eta^2\text{-}H_2C{=}CHMe)Cl_2$ (**9**)[49] and which could be analyzed in situ via ^{13}C NMR spectroscopy. To this end, a solution of **1a**-3,4,5-$^{13}C_3$·HBF_4 (44 mM) and **9** (2 equiv) in $CDCl_3$ was sparged with N_2 for 2.5 h to form a ~4:1 mixture of **8a**-3,4,5-$^{13}C_3$·HBF_4 and the platinamethylpyrrolidinium isotopomer **5a**-$^{13}C_3$ as the only ^{13}C-labeled compounds detected by ^{13}C NMR spectroscopy (Scheme 6). The formation of **8a**-3,4,5-$^{13}C_3$·HBF_4 was established by the large upfield shifts and reduced $^1J_{C=C}$ coupling constant for the alkene carbon atoms of **8a**-3,4,5-$^{13}C_3$·HBF_4 (δ 92.5 (t, J = 42.4 Hz), 73.0 (d, J = 43.2 Hz)) relative to those of **1a**-3,4,5-$^{13}C_3$·HBF_4 (δ 131.5 (dd, J = 43, 69 Hz), 120.6 (d, J = 69 Hz)). Addition of triethylamine (4 equiv) to **8a**-3,4,5-$^{13}C_3$·HBF_4 at 25 °C resulted in immediate (≤3 min) formation of azaplatinacyclobutane **6a**-$^{13}C_3$ with no detectable formation of **4a**-3,4,5-$^{13}C_3$ (Scheme 5).[50] This observation establishes a mechanism for the conversion of **4a** to **5a** involving rate-limiting intramolecular ligand exchange to form **8a** followed by rapid outer-sphere attack of amine on the coordinated C=C bond of **8a** to form **5a**. The activation parameters

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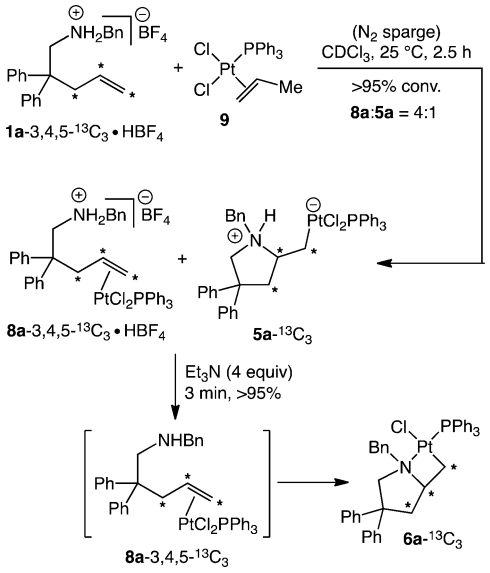
Scheme 6



determined for the conversion of **4a** to **5a** therefore correspond specifically to the irreversible conversion of **4a** to **8a**.

Nature of the Platinum−Alkene Bond in 8a-3,4,5-$^{13}C_3$·HBF$_4$. One-bond carbon−carbon coupling constants are roughly proportional to the sum of the σ character of the two carbon atoms. For example, $^1J_{C=C} \approx 70$ Hz for a C(sp^2)−C(sp^2) bond while $^1J_{C=C} \approx 35$ for a C(sp^3)−C(sp^3) bond.[51] For this reason, the $^1J_{C=C}$ coupling constant of an alkene bound to a transition metal serves as a sensitive measure of d → π^* back-bonding,[52] which at the extreme leads to complete $sp^2 \rightarrow sp^3$ rehybridization of the alkene carbon atoms with predominant metallacyclopropane character (Figure 5). As points of comparison, the $^1J_{C=C}$

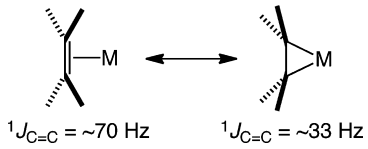
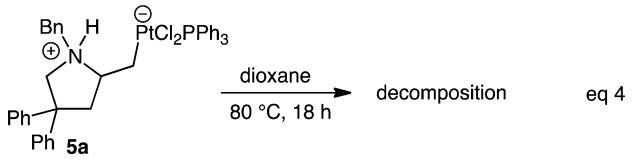


Figure 5. π-Alkene and metallacyclopropane bonding contributors and anticipated limiting one-bond carbon−carbon coupling constants.

value of **8a**-3,4,5-$^{13}C_3$·HBF$_4$ (42.4 Hz) is significantly larger than that of the electron-rich platinum(0) π-ethylene complex $(PCy)_2Pt(\eta^2\text{-}H_2C{=}CH_2)$ ($^1J_{C=C}$ = 31 Hz),[53] slightly smaller than that of the cationic Pd(II) chelate complex {(phen)Pd-[η^1,η^2-CH(CH$_2$SiEt$_3$)CH$_2$C(CO$_2$Me)$_2$CH$_2$CH=CH$_2$]}$^+$[BAr$_4$]$^-$ (Ar = 3,5-C$_6$H$_3$(CF$_3$)$_2$; $^1J_{C=C}$ = 47 Hz),[54] and significantly smaller than that of the cationic gold(I) complex [(IPr)Au(η_2-H$_2$C=CMe$_2$)]$^+$SbF$_6^-$ (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine; $^1J_{C=C}$ = 66 Hz).[55] These data suggest that the electrophilicity of cationic Pt(II) complexes is similar to that of cationic Pd(II) complexes but markedly less than that of cationic, two-coordinate gold π complexes, consistent with the results of Hammett analysis of vinyl arene binding affinities for cationic Pd(II), Pt(II), and Au(I) complexes.[55−57]

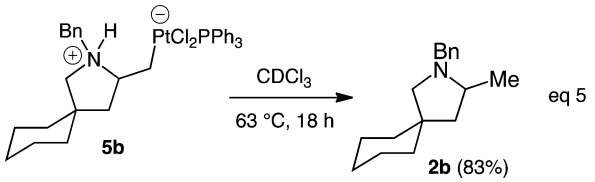
Protodemetalation of Complexes 5 and 6. We envisioned pathways for product formation in the platinum-catalyzed hydroamination of **1** involving either intramolecular protonolysis of platinamethylpyrrolidinium complexes **5** or intermolecular protonolysis of azaplatinacyclobutanes **6** with an ammonium salt. Of these two potential pathways, intramolecular protodemetalation of a β-ammonioethanide intermediate has been invoked as the product-releasing step in a number of late-transition-metal-catalyzed alkene hydroamination processes.[10,11,14,15,19,43] Conversely, azametallacyclobutanes have rarely been invoked as intermediates in late-transition-metal-catalyzed alkene hydroamination,[24,25] and product-releasing protodemetalation of an azametallacyclobutane has not been documented. Casalnuovo isolated the azairidacyclobutane hydride complex Ir(PEt$_3$)$_2$(NHPhC$_7$H$_{10}$)(H)Cl from reaction of aniline and norbornene with Ir(PEt$_3$)$_2$(C$_2$H$_4$)$_2$Cl that underwent C−H reductive elimination to form *exo*-2-(phenylamino)-norbornane.[24] Similarly, Hartwig invoked the intermediacy of an azarhodiacyclobutane in the anti-Markovnikov hydroamination of vinylarenes with alkyl amines catalyzed by cationic rhodium DPEphos complexes (DPEphos = (oxidi-2,1-phenylene)bis-(diphenylphosphine)) that was presumably consumed via C−H reductive elimination.[25]

Several experiments were performed to evaluate the reactivity of platinamethylpyrrolidinium complexes **5** with respect to intramolecular protodemetalation. For example, thermolysis of a dioxane-d_8 solution of platinamethylpyrrolidinium complex **5a** (32 mM) at 80 °C for 18 h led to decomposition without formation of detectable quantities of **2a** (eq 4). In contrast,



eq 4

heating a solution of **5b** in $CDCl_3$ at 63 °C for 18 h formed pyrrolidine **2b** in 80% yield by ^{1}H NMR analysis (eq 5);



eq 5

chloroform was employed in this experiment, owing to the low solubility of **5b** in dioxane/diglyme mixtures. In a separate experiment, a solution of **5b** (50 mM) in $CDCl_3$ at 54 °C was monitored periodically by ^{1}H NMR spectroscopy. Disappearance of **5b** obeyed first-order kinetics through ~1 half-life with an observed rate constant of $k_{obs} = 2.8 \times 10^{-5}$ s^{-1} (Figure S1 in the Supporting Information).

Several experiments were likewise performed to evaluate the reactivity of azaplatinacyclobutanes **6** toward protodemetalation with alkyl ammonium salts. In one experiment, heating an equimolar mixture of **6a** (32 mM) and benzyl-4-pentenylammonium chloride (generated in situ from reaction of **5a** and benzyl-4-pentenylamine) at 120 °C for 16 h formed **2a** in quantitative yield by ^{1}H NMR analysis (eq 6). Similarly, heating a 1:1 solution of **6b** and triethylammonium chloride (50 mM) in diglyme/dioxane-d_8 (85/15 v/v) at 78 °C for 12 h led to protodemetalation to form pyrrolidine **2b** in 83% yield (^{1}H NMR; eq 7). In a separate experiment, a solution of **6b** (64 mM) and HNEt$_3$BF$_4$ (0.46 M) in diglyme/dioxane-d_8 (85/15 v/v) was heated at 78 °C and monitored periodically by ^{31}P NMR spectroscopy.[58] A plot of ln[**6b**] versus time was linear through

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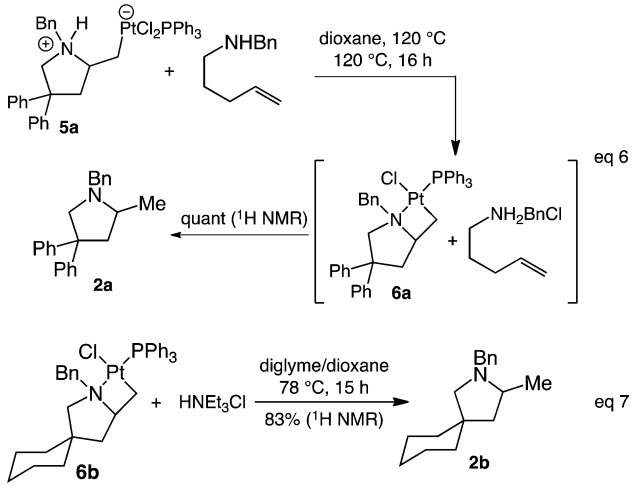


~85% conversion with a first-order rate constant of $k_{obs} = (9.37 \pm 0.07) \times 10^{-5}$ s^{-1} (Figure 6). In a similar manner, first-order rate

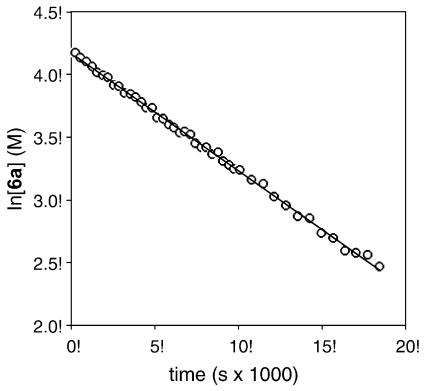


Figure 6. First-order plot for the protodemetalation of **6b** (64 mM) and $HNEt_3BF_4$ (0.64 M) at 78 °C in diglyme/dioxane-d_8 (85/15 v/v).

constants were determined as a function of ammonium ion concentration from 0.10 to 0.64 M. The resulting plot of k_{obs} versus $[HNEt_3BF_4]$ was linear with a significant nonzero intercept (Figure 7), which points to a two-term rate law for

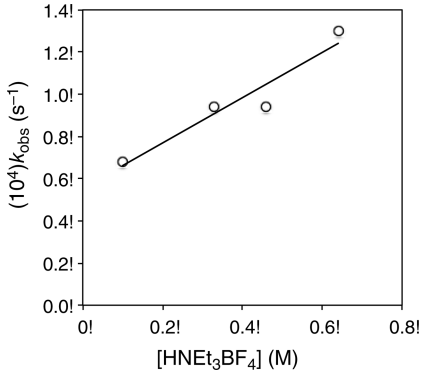


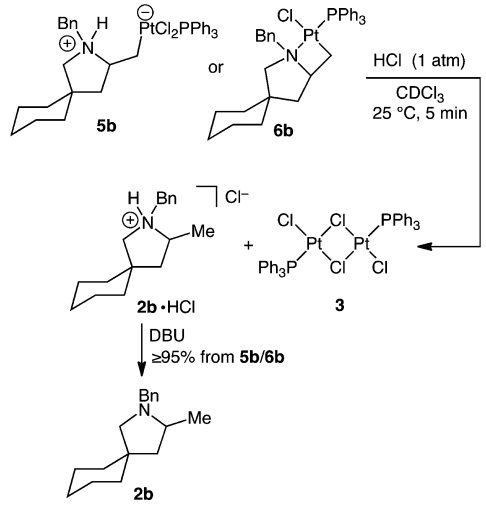
Figure 7. Ammonium ion concentration dependence of the protodemetalation of **6b** (64 mM) and $[HNEt_3]BF_4$ (0.10–0.64 M) at 78 °C in diglyme/dioxane-d_8 (85/15 v/v).

protodemetalation of **6b**: rate = $k_1[\mathbf{6b}] + k_2[\mathbf{6b}][HNEt_3BF_4]$, where $k_1 = (6 \pm 1) \times 10^{-5}$ s^{-1} ($\Delta G^{\ddagger}_{351\,K}$ = 27.5 kcal/mol) and $k_2 = (1.1 \pm 0.2) \times 10^{-4}$ M^{-1} s^{-1} ($\Delta G^{\ddagger}_{351\,K}$ = 27.0 kcal/mol).

As a direct comparison to the intramolecular protodemetalation of **5b**, we determined the rate of protodemetalation of a 1:1 mixture of **6b** and $EtNHBF_4$ (50 mM) in $CDCl_3$ at 54 °C. Disappearance of **6b** reactions obeyed first-order kinetics through 1 half-life with observed rate constants of $k_{obs} = 1.7 \times 10^{-5}$ s^{-1} (Figure S1 in the Supporting Information), which is roughly 60% of that observed for intramolecular protodemetalation of **5b** under comparable conditions.

In a final set of experiments, treatment of either **5b** or **6b** with anhydrous HCl (1 atm, 0.11 mmol) in $CDCl_3$ at 25 °C for 5 min led to complete consumption to form the pyrrolidinium chloride **2b**·HCl and platinum chloride dimer **3** as the exclusive products. Basification of the resulting solutions with DBU (1,8-diazabicyclo-5.4.0 undec-7-ene) produced free pyrrolidine **2b** in ≥95% yield (Scheme 7). In a separate experiment, a $CDCl_3$ solution of **6b**

Scheme 7



and HCl (1 atm, 0.11 mmol) was generated at −50 °C and analyzed periodically by ^{1}H and ^{31}P NMR spectroscopy. No change was observed at −50 °C, but as the solution was warmed slowly, resonances corresponding to the pyrrolidinium product **2b**·HCl began to appear at 0 °C and continued warming to 25 °C formed **2b**·HCl and **3** as the exclusive products (Scheme 7). Throughout complete conversion of **6b** to **2b**·HCl, no resonances were observed that could be attributed to either a platinum hydride complex or to zwitterionic complex **5b**.

Analysis of Catalytic Mixtures of 1 and 3. In an effort to identify the resting state in the platinum-catalyzed hydroamination of 4-pentenylamines, a solution of **1a** (0.25 M) and **3** (2.5 mol %) in diglyme-d_{14} was monitored periodically by ^{1}H NMR spectroscopy at 120 °C. Resonances corresponding to **6a** or the corresponding ammonium chloride adduct **6b**·R_3NHCl (R_3N = **1b** or **2b**; see below) were observed within the first ~5% of conversion, persisted throughout ~95% conversion of **1a** to **2a**, and disappeared upon complete consumption of **1a** (eq 8). Similarly, ^{1}H NMR analysis of a solution of **1b** and **3** in diglyme-d_{14} at 80 °C established azaplatinacyclobutane **6b** as the only organometallic species present during the complete conversion of **1b** to **2b** (eq 8).

The exclusive accumulation of azaplatinacyclobutane complexes **6a**,**b** during the platinum-catalyzed hydroamination of **1a**,**b**, respectively, established complexes **6** as the catalyst resting states and protodemetalation of **6** as the turnover-limiting step of catalysis. An alternative scenario involving reversion of **6** to **5**

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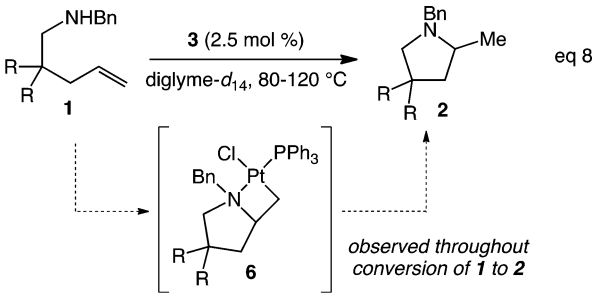
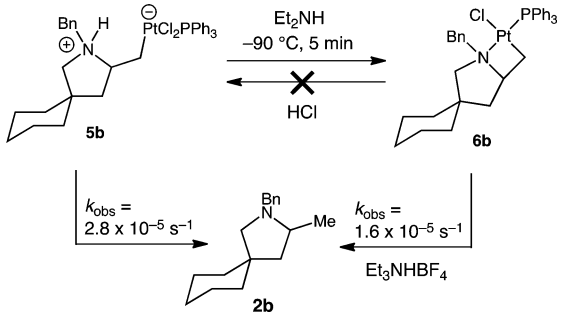


followed by protodemetalation of **5** (in which case **6** would be an off-cycle catalyst reservoir) can be discounted on the basis of our stoichiometric experiments involving the protodemetalation of **5** and **6**. In the case of the conversion of **1a** to **2a**, protodemetalation of **5a** under catalytic conditions is readily discounted, owing to the failure of **5a** to undergo intramolecular protodemetalation. In the case of the conversion of **1b** to **2b**, although our experiments established the viability of the protodemetalation of **5b**, the rate of protodemetalation of **5b** was not sufficient to compete with the extremely facile (~5 min at −90 °C) and exergonic conversion of **5b** to **6b** in the presence of amine base, such as under catalytic conditions (Scheme 8).

Scheme 8. Comparison of Rates for the Conversion of 5b to 6b and for the Protodemetalation of 5b and 6b in CD_2Cl_2 or $CDCl_3$



In particular, the failure to observe detectable quantities of **5b** from the reaction of **6b** and HCl suggests that the equilibrium for the conversion of **5b** and amine to form **6b** and ammonium chloride lies far to the right, as was established by Green for the reactions of $(PPh_3)PtCl_2(\pi\text{-}H_2C{=}CH_2)$ with secondary amines ($K \approx 1 \times 10^6$ M^2).[39] Therefore, for the protodemetalation of **5b** to be catalytically relevant, the rate of protodemetalation of **5b** would need to be orders of magnitude faster than protodemetalation of **6b** with ammonium salt, and a side by side comparison of the protodemetalation of **5b** and **6b** strongly suggests that this is not the case (Scheme 8).

Kinetics of Catalytic Hydroamination. We sought to determine the rate behavior of the catalytic hydroamination of **1** under conditions that approximated the relative and absolute concentrations employed in preparative-scale reactions.[7] To this end, a solution of **1b** (0.42 M) and **3** (16 mM; [Pt] = 32 mM) in diglyme at 120 °C was monitored periodically by GC. A plot of [**1b**] versus time was linear through ~2.5 half-lives and displayed positive curvature at higher conversion, which established the zeroth-order dependence of the rate on [**1b**] over the concentration range 0.42−0.1 M with a pseudo-zeroth-order rate constant of k_{obs} = (1.99 ± 0.04) × 10^{-3} M s^{-1} (Figure 8).

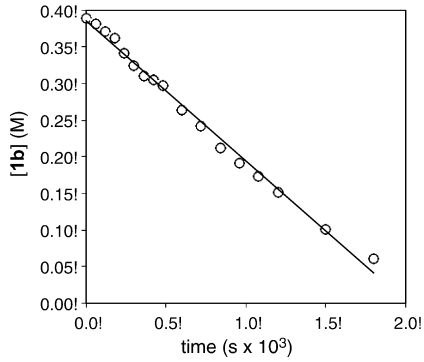


Figure 8. Pseudo-zeroth-order plot for the conversion of **1b** (0.42 M) to **2b** catalyzed by **3** (16 mM) in diglyme at 120 °C.

To determine the rate dependence on catalyst concentration, pseudo-zeroth-order rate constants for the platinum-catalyzed hydroamination of **1b** were determined as a function of [**3**] from 5.5 to 21 mM. A plot of ln[k_{obs}] versus ln[Pt] ([Pt] = 2[**3**]) was linear with a slope of 1.14 ± 0.08 (Figure 9), which indicated a

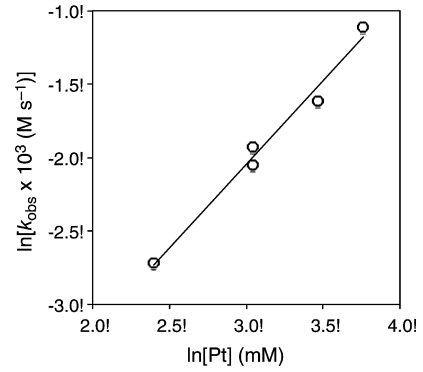


Figure 9. Plot of ln(k_{obs}) versus ln[Pt] (Pt = 2[**3**]) for the conversion of **1b** (0.42 M) to **2b** catalyzed by **3** (5.5−22 mM) in diglyme at 120 °C (slope 1.14 ± 0.08).

slightly greater than first-order dependence of the rate on catalyst concentration. To estimate the free energy of activation for the platinum-catalyzed hydroamination of **1b**, a plot of k_{obs} versus [Pt] provided a first-order rate constant of k_1 = (7.5 ± 0.6) × 10^{-3} s^{-1} (Figure S2 in the Supporting Information), which corresponds to the free energy of activation of $\Delta G^{\ddagger}_{393\,K}$ = 27 kcal/mol.

Kinetic analysis of the catalytic hydroamination of **1b** catalyzed by **3** pointed to a kinetic scenario that approached the first-order rate law: rate = k[Pt]. Given the identification of **6b** as the catalyst resting state and protodemetalation of **6b** as the turnover-limiting step of the platinum-catalyzed conversion of **1b** to **2b**, the nominal first-order dependence of the rate on platinum concentration was unanticipated and argues against a bimolecular pathway for protodemetalation. Specifically, because ammonium salt is formed concomitantly with azaplatinacycle **6b** under catalytic conditions and because azaplatinacyclobutane **6b** accounted for all of the platinum introduced as **3**, [ammonium ion] ≈ [**6b**] ≈ $[Pt]_{tot}$ under catalytic conditions. Therefore, a mechanism involving turnover-limiting, intermolecular protodemetalation of **6b** with ammonium salt would display second-order rate dependence on [Pt] (rate = k[Pt]^2), which was not observed (Scheme 9).[23] Rather, the approximately first-order dependence of the rate on platinum concentration (rate ≈ k[Pt])

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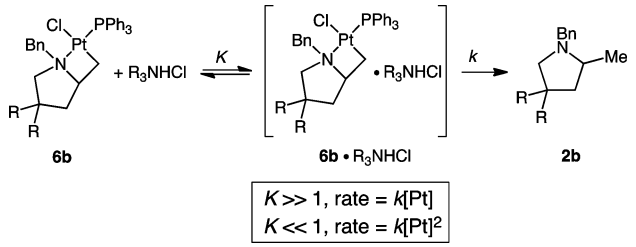
Scheme 9



requires a pathway for consumption of **6** that is largely independent of ammonium ion concentration.

To account for the near zeroth-order dependence of the rate of catalytic hydroamination on ammonium ion concentration, we initially considered a scenario for protodemetalation of **6** involving rate-limiting ligand dissociation to generate a neutral or cationic three-coordinate species that was trapped by ammonium ion. However, it appears unlikely that reaction of the three-coordinate platinum species with ammonium ion would be fast enough relative to ligand recombination to realize approximately zeroth-order dependence in ammonium ion concentration.

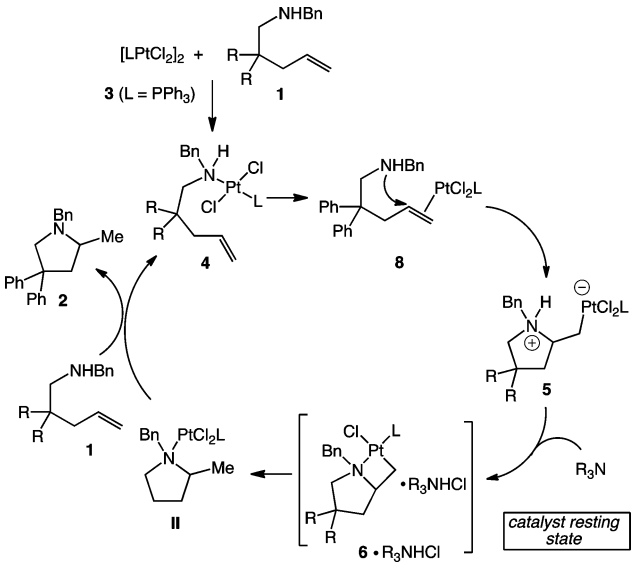
An alternative mechanism that accounts for the near-first-order dependence of the rate of catalytic hydroamination on catalyst concentration is suggested by Green's observations regarding the formation of discrete azaplatinacyclobutane-ammonium chloride adducts such as **7**·Et_2NH_2Cl. Specifically, we suggest a mechanism involving turnover-limiting, intramolecular protodemetalation of the azaplatinacyclobutane-ammonium chloride adduct **6b**·R_3NHCl (R_3N = **1b**, **2b**) generated from **6b** and the ammonium chloride salt under catalytic conditions (Scheme 9). Provided that the equilibrium constant K for the formation of **6b**·R_3NHCl from **6b** and R_3NHCl is sufficiently large (i.e., $[Pt]_{tot} \approx [\mathbf{6b}\cdot R_3NHCl]$) as is suggested by Green's work,[35,39,40] and intramolecular protodemetalation represents the lowest energy pathway for protodemetalation, catalytic hydroamination should display first-order rate dependence on [Pt] and zeroth-order dependence on [**1b**], consistent with the experimentally determined rate law rate $\approx k[Pt]$. The slightly greater than first-order rate dependence on [Pt] points to the contribution of an ammonium ion dependent pathway for protodemetalation in the catalytic hydroamination of **1b**. Indeed, to the extent that K is not sufficiently large to achieve the condition $[Pt]_{tot} \approx [\mathbf{6b}\cdot R_3NHCl]$, the rate of catalytic hydroamination displays dependence on ammonium ion concentration, which is manifested as greater than first-order dependence on [Pt] (Scheme 9).

Although Green did not speculate on the nature of the azaplatinacyclobutane–ammonium ion adduct, neither he nor we noted any spectral changes in the presence or absence of ammonium salt. Given this observation, the most reasonable structure for an **6b**·R_3NHCl adduct is that generated via hydrogen bonding of the ammonium proton to the chloride ligand of **6**. Brammer and others have shown that chloride ligands of late-transition-metal complexes, platinum in particular, are good hydrogen bond acceptors and form particularly robust hydrogen bonds with ammonium salts.[59−61] Indeed, hydrogen bonding to Pt–Cl bonds has been exploited as a construct in crystal engineering.[60] In the case of **6b**·R_3NHCl, the platinum-bound chloride would have to compete with exogenous Cl^-, which is typically a stronger hydrogen bond acceptor than is a M–Cl bond.[59,62] However, the presence of a strong σ-donor alkyl ligand trans to the chloride ligand in **6**,[47] which is reflected in the long Pt–Cl bond (2.41 Å), may enhance the hydrogen bond acceptor ability of the chloride ligand to the extent that it competes effectively with exogenous Cl^-. Because of the preferred 90° angle of the Pt–Cl···H hydrogen bond,[59] association of the ammonium ion via hydrogen bonding would properly orient the proton for transfer to Pt to generate a reactive Pt(IV) hydride species which is a potential intermediate in the protodemetallation event (see below).[63]

Importantly, the free energy of activation for the catalytic conversion of **1b** to **2b** ($\Delta G^{\ddagger}_{393\,K}$ = 27 kcal/mol) was similar to that determined for the ammonium ion independent pathway in the protodemetalation of **6** with triethylammonium salt ($\Delta G^{\ddagger}_{393\,K}$ = 27 kcal/mol). Although stoichiometric protodemetalation of **6b** pointed to the presence of competing ammonium ion dependent and independent pathways, the ammonium ion dependent pathway in these reactions presumably corresponds to the intermolecular protodemetalation of the azaplatinacyclobutane–ammonium ion adduct **6b**·Et_3NHBF_4 and is not likely relevant to the catalytic hydroamination of **1b**. In this regard, it must be noted that the kinetics of the protodemetalation of **6b** under stoichiometric conditions were determined at ammonium ion concentrations ([R_3NHCl] = 0.10–0.64 M) that far exceed those realized under catalytic conditions ([R_3NHCl] = 11–42 mM). Rather, extrapolation of the ammonium ion dependent pathway for the stoichiometric protodemetalation of **6b** to catalytically relevant ammonium ion concentrations predicts no significant (<10%) contribution of this pathway under catalytic conditions.

Mechanism of Catalytic Hydroamination. All of our experimental observations, including (1) the irreversible formation of platinum π-alkene complex **8a**, (2) the net anti addition of platinum and amine across the C=C bond of **8a**, (3) the identification of azaplatinacycle **6** as the catalyst resting state, and (4) the nominal first-order rate law for the catalytic hydroamination of **1b** (rate $\approx k[Pt]$), are consistent with the mechanism for the intramolecular hydroamination of benzyl 4-pentenylamines **1** catalyzed by **3** depicted in Scheme 10.

Scheme 10



The catalytic cycle is first accessed via the bridge-splitting reaction of **3** with **1** to form the nitrogen-bound platinum 4-pentenylamine complex **4**. Complex **4** undergoes irreversible

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intramolecular ligand exchange ($\Delta G^{\ddagger}_{301\,K}$ = 21.45 kcal mol^{-1} for **4a**) to generate the unobserved platinum alkene complex **8**, which undergoes rapid outer-sphere C−N bond formation to form the zwitterionic platinamethylpyrrolidinium complex **5**. Rapid and exergonic deprotonation of **5** with free amine (R_3N = **1**, **2**) forms the azaplatinacyclobutane complex **6**, which presumably exists as the discrete 1:1 azaplatinacyclobutane−ammonium chloride adduct **6**·R_3NHCl in the nonpolar reaction medium (Scheme 10). The facile and exergonic conversion of both **8** to **5** and **5** to **6** likely renders C−N bond formation irreversible under reaction conditions. The azaplatinacyclobutane−ammonium adduct **6**·R_3NHCl represents the catalyst resting state and is consumed via turnover-limiting intramolecular protonolysis ($\Delta G^{\ddagger}_{393\,K}$ = 27 kcal/mol), presumably through an unobserved Pt(IV) hydride intermediate followed by reductive elimination,[63] to form the unobserved platinum pyrrolidine complex **II**. Associative ligand exchange of **1** with **II** would release **2** and regenerate the nitrogen-bound platinum 4-pentenylamine complex **4** (Scheme 10).

CONCLUSIONS

In summary, we have investigated the mechanism of the platinum-catalyzed intramolecular hydroamination of 2,2-disubstituted benzyl 4-pentenylamines to form 2-methylpyrrolidines. Our investigation included the independent generation and evaluation of potential intermediates, stereochemical analysis of C−N bond formation, identification of the catalyst resting state and turnover-limiting step, and kinetic analysis of catalytic hydroamination. Together, these data support the mechanism depicted in Scheme 10, involving as key steps the outer-sphere addition of the pendant amine on the coordinated C=C bond of platinum π-alkene complex **8** and turnover-limiting intramolecular protodemetalation of the 1:1 azaplatinacyclobutane−ammonium ion adduct **6**·R_3NHCl.

Turnover-limiting protodemetalation appears to be a general feature of late-transition-metal-catalyzed hydroamination of alkenes with alkylamines, presumably owing to the high nucleophilicity of the amine, which facilitates C−N bond formation and weak Brønsted acidity of the resulting ammonium salt, which retards the rate of protodemetalation. A notable exception is the intramolecular hydroamination of primary aminoalkenes catalyzed by a rhodium aminophosphine complex reported by Hartwig that occurs via turnover-limiting C−N bond formation.[11] Although the platinum-catalyzed intramolecular hydroamination of 4-pentenylamines follows this general trend, the turnover-limiting protodemetalation of the azametallacyclobutane **6** is perhaps the most distinctive feature of the catalytic cycle. Indeed, the turnover-limiting protodemetalation of an azametallacyclobutane intermediate under conditions of catalytic hydroamination has not previously been documented. A second notable mechanistic feature of the platinum-catalyzed hydroamination of 4-pentenylamines is the facile ($\Delta G^{\ddagger} \approx 21$ kcal mol^{-1}) irreversible conversion of the *N*-bound 4-pentenylamine complex **4** to the π-bound species **8**, which avoids amine inhibition of catalysis despite the greater binding affinity of the secondary amine to Pt(II) relative to the monosubstituted C=C bond.

EXPERIMENTAL SECTION

Synthesis of Platinum Complexes 4a−6a. *$(PPh_3)Pt\{\kappa^1$-N-$[NH(Bn)CH_2C(Ph)_2CH_2CH{=}CH_2]\}Cl_2$ (**4a**).* A frozen suspension of **1a** (5.4 mg, 1.7 × 10^{-2} mmol), phenyltrimethylsilane (0.32 mg, 2.1 × 10^{-3} mmol), and **3** (8.9 mg, 8.4 × 10^{-3} mmol) in $CDCl_3$ (1.16 mL) at −78 °C was thawed briefly to form a yellow solution that was placed into the probe of an NMR spectrometer precooled at −20 °C. ^{1}H NMR analysis of the resulting solution after 5 min revealed complete consumption of **1a** to form **4a** in 97% yield, determined by integrating the olefinic resonances of **4a** at δ 5.90−5.98 (H_5), 5.09 (H_7), and 4.98 (H_6) relative to the methyl resonance of $PhSiMe_3$ at δ 0.02. Thermally unstable **4a** was characterized without isolation by 1D ^{1}H, ^{1}H{^{31}P}, and ^{31}P NMR spectroscopy, by 2D ^{1}H−^{1}H COSY and ^{1}H−^{1}H NOESY spectroscopy (Figures S3−S6 in the Supporting Information), and through NMR analysis of the isotopomers $(PPh_3)Pt\{\kappa^1$-*N*-$[^{15}NH(Bn)CH_2C(Ph)_2CH_2CH{=}CH_2]\}Cl_2$ (**4a**-^{15}N) and $(PPh_3)Pt\{\kappa^1$-*N*-$[NH(Bn)CH_2C(Ph)_2{}^{13}CH_2{}^{13}CH{=}{}^{13}CH_2]\}Cl_2$ (**4a**-$^{13}C_3$). The numbering scheme for the aliphatic ^{1}H resonances of **4a** is depicted in Figure 10. ^{1}H{^{31}P} NMR (500 MHz, −20 °C): δ 6.84−7.82 (m, 30 H), 5.90−5.98 (m, 1 H, H_5), 5.09 (d, J = 16.9 Hz, 1 H, H_7), 4.98 (d, J = 10.3 Hz, 1 H, H_6), 4.57 (dd, J = 8.0, 12.5 Hz, 1 H, H_3), 4.52 (dd, J = 6.6, 12.7 Hz, 1 H, H_1), 4.13 (dd, J = 5.9, 14.1 Hz, 1 H, H_4), 3.81 (t, J = 7.1 Hz, 1 H, H_2), 3.44 (dd, J = 7.3, 12.8 Hz, 1 H, H_1), 3.12−3.19 (m, 2 H, H_3 + H_4). ^{31}P{^{1}H} NMR (−20 °C): δ 5.20 (s, J_{PtP} = 3566 Hz).

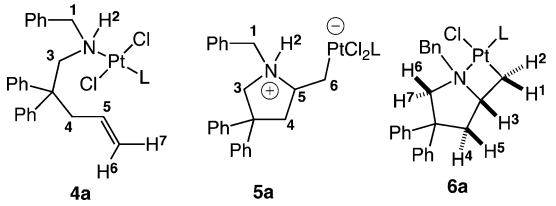

Figure 10. Numbering scheme for the ^{1}H resonances of compounds **4a**−**6a**.

*$(PPh_3)Pt[CH_2CHNH(Bn)CH_2CPh_2CH_2]Cl_2$ (**5a**).* A solution of **4a** (~1.7 × 10^{-2} mmol, ~29 mM) and phenyltrimethylsilane (0.32 mg, 2.1 × 10^{-3} mmol) in $CDCl_3$ (580 μL) was warmed to 28 °C for 1 h to form **5a** in 94 ± 5% yield, as determined by integrating the benzylic resonance of **5a** at δ 5.25 relative to the methyl resonance of $PhSiMe_3$ at δ 0.02. In a separate experiment, a solution of **1a** (25 mg, 0.076 mmol) and **3** (41 mg, 0.039 mmol) in $CDCl_3$ (3 mL) was maintained at room temperature for 4 h. Solvent was evaporated under vacuum to give pure **5a** (66 mg, 100%) as a tan solid. Complex **5a** was characterized by 1D ^{1}H{^{31}P}, ^{13}C{^{1}H}, and ^{31}P NMR spectroscopy, by 2D ^{1}H−^{1}H COSY NMR spectroscopy (Figures S7 and S8 in the Supporting Information), by mass spectrometry, and by NMR analysis of isotopomers $(PPh_3)Pt[CH_2CH^{15}NH(Bn)CH_2CPh_2CH_2]Cl_2$ (**5a**-^{15}N) and $(PPh_3)Pt[^{13}CH_2{}^{13}CHNH(Bn)CH_2CPh_2{}^{13}CH_2]Cl_2$ (**5a**-$^{13}C_3$). The numbering scheme for the aliphatic ^{1}H resonances of **5a** is depicted in Figure 10. ^{1}H NMR (500 MHz): δ 10.11 (br s, 1 H, H_2), 7.82 (dd, J = 7.5, 11.3 Hz, 6 H), 7.14−7.48 (m, 20 H), 7.05 (d, J = 7.7 Hz, 2 H), 6.89 (d, J = 7.2 Hz, 2 H), 5.25 (dd, J = 2.8, 12.3 Hz, 1 H, H_3), 3.75−3.88 (m, 2 H, H_1), 2.72 (dd, J = 5.6, 14.0 Hz, 1 H, H_4), 2.62 (dd, J = 10.0, 12.8 Hz, 1 H, H_3), 2.39−2.52 (m, 1 H, H_5), 2.08 (dd, J = 11.2, 13.6 Hz, 1 H, H_4), 1.94 (t, J = 11.1 Hz, 1 H, H_6), 1.42 (ddd, J = 3.6, 6.4, 12.0 Hz, 1 H, H_6). ^{13}C{^{1}H} NMR: δ 144.3, 142.5, 134.9, 134.8, 130.9, 130.6, 130.6, 130.3, 130.3, 129.9, 129.7, 129.5, 129.4, 128.9, 128.1, 128.0, 128.0, 127.2, 126.7, 125.7, 73.9, 59.5, 57.6, 54.7, 46.0, 8.4. ^{31}P{^{1}H} NMR: δ 14.19 (s, J_{PtP} = 4844 Hz). ESI-MS calcd (found) for $C_{42}H_{40}ClNPPt^+$ (M^+ − Cl): 820.3 (820.2).

*Kinetics of the Conversion of **4a** to **5a**.* An NMR tube containing a solution of **1a** (6.0 mg, 1.8 × 10^{-2} mmol), phenyltrimethylsilane (20 μL of stock (50 μL in 3 mL of $CDCl_3$), 1.9 × 10^{-3} mmol) in $CDCl_3$ (580 μL) was placed in the probe of an NMR spectrometer maintained at 28 °C. After 5 min, the tube was ejected, **3** (17.9 mg, 1.69 × 10^{-2}) was added, the tube was returned to the spectrometer, and data acquisition began. Data points were acquired every 109 s. The concentration of **4a** was determined by integrating the allylic resonance of **4a** at δ 4.13 (H_4) relative to the methyl resonance of $PhSiMe_3$ at δ 0.02. A plot of ln[**4a**] versus time was linear to ≥3 half-lives with

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slope = (1.66 ± 0.02) × 10^{-3} s^{-1} (Figure 3). Employing a similar procedure, the first-order rate constants for the conversion of **4a** to **5a** were determined in duplicate at 7.3, 11.8, 17.3, 22.9, 33.9, and 39.5 °C with all rates being determined by linear regression analysis over 2 half-lives (Table S1 in the Supporting Information). A plot of ln (k/T) versus 1/T was linear with slope = −6550 (Figure 4).

*(PPh$_3$)Pt{κ^2-C,N-[CH$_2$CHN(Bn)CH$_2$CPh$_2$CH$_2$]Cl (**6a**).* Diethylamine (3.4 μL, 3.3 × 10^{-2} mmol) was placed in an NMR tube containing a solution of **5a** (3.3 × 10^{-2} mmol, 33 mM) and $PhSiMe_3$ (1 μL, 6 × 10^{-3} mmol) in $CDCl_3$ (1.00 mL), and the tube was shaken briefly. ^1H NMR analysis of the resulting solution within 5 min of mixing revealed formation of **6a** in 104 ± 5% yield, as was determined by integrating the benzylic resonance of **6a** at δ 5.04 relative to the methyl resonance of $PhSiMe_3$ at δ 0.02. In a separate experiment, a solution of **1a** (149 mg, 0.455 mmol) and **3** (243 mg, 0.230 mmol) in $CHCl_3$ (12 mL) was stirred overnight at room temperature. Diethylamine (190 μL, 1.83 mmol) was added, and the resulting mixture was stirred for 15 min and diluted with $CHCl_3$ (30 mL). The reaction mixture was washed with water (3 × 25 mL), 0.1 M HCl (3 × 15 mL), and brine (15 mL), dried ($MgSO_4$), and concentrated to ∼10 mL. Pentane (200 mL) was added, and the mixture was cooled to −10 °C overnight. The resultant off-white powder was isolated by vacuum filtration, washed with pentane (50 mL), and dried under vacuum to yield **6a** (211 mg, 64%). Complex **6a** was characterized by 1D $^1H\{^{31}P\}$, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectroscopy, by 2D $^1H-^1H$ COSY NMR (Figures S9 and S10 in the Supporting Information) and $^1H-^1H$ NOE spectroscopy (Figure S11 in the Supporting Information), by mass spectrometry, and by NMR analysis of isotopomers (PPh$_3$)Pt{κ^2-C,N-[CH$_2$CH^{15}N(Bn)CH$_2$CPh$_2$CH$_2$]Cl (**6a**-^{15}N) and (PPh$_3$)Pt{κ^2-C,N-[^{13}CH$_2$^{13}CHN(Bn)CH$_2$CPh$_2$^{13}CH$_2$]Cl (**6a**-$^{13}C_3$). The numbering scheme for the aliphatic ^1H resonances of **6a** is depicted in Figure 10. ^1H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 7.0 Hz, 2 H), 7.51 (d, J = 7.5 Hz, 2 H), 7.17−7.44 (m, 25 H), 7.06 (t, J = 7.1 Hz, 1 H), 5.26−5.32 (m, 1 H, H_3), 5.04 (dd, J = 4.0, 12.5 Hz, 1 H, −CH_2Ph), 4.56 (d, J = 11.4 Hz, 1 H, H_7), 3.85 (dd, J = 2.9, 12.5 Hz, 1 H, − CH_2Ph), 3.35 (dd, J = 8.3, 11.8 Hz, 1 H, H_6), 3.04 (dd, J = 7.8, 13.3 Hz, 1 H, H_5), 2.48 (dd, J = 7.5, 13.5 Hz, 1 H, H_4), 0.06 (ddd, J_{PH} = 1.8 Hz, J = 3.5, 9.1, 1 H, H_1), −0.34 (ddd, J_{PH} = 4.0 Hz, J = 8.6, 9.1 Hz, 1 H, H_2). $^{13}C\{^1H\}$ NMR: δ 146.1, 145.8, 135.1, 134.4, 134.3, 133.0, 131.5, 130.9, 130.2, 130.1, 128.9, 128.6, 128.2, 128.1, 127.9, 127.8, 127.1, 126.6, 126.6, 126.3, 76.3, 68.4, 63.1, 55.2, 45.9, −13.0. $^{31}P\{^1H\}$ NMR: δ 11.09 (s, J_{PtP} = 4402 Hz). ESI-MS calcd (found) for $C_{42}H_{39}NPPt$ (M^+ − Cl): 783.2 (783.3).

(PPh$_3$)Pt[η^2-^{13}CH$_2$═^{13}CH^{13}CH$_2$C(Ph)$_2$CH$_2$NHBn]Cl$_2$·HBF$_4$ (8a-3,4,5-$^{13}C_3$). A solution of **1a**-$^{13}C_3$·HBF_4 (11 mg, 2.7 × 10^{-2} mmol) and *cis*-(PPh$_3$)Pt(η^2-H$_2$C═CHMe)Cl$_2$ (**9**; 30 mg, 5.3 × 10^{-2} mmol) in $CDCl_3$ (0.60 mL) was continually sparged with N_2 for 2.5 h to form a 4:1 mixture of **8a**-3,4,5-$^{13}C_3$ and **5a**-$^{13}C_3$, which were the only isotopically labeled compounds detected in solution. Complex **8a**-3,4,5-$^{13}C_3$ was analyzed in solution by ^{13}C and ^{31}P NMR spectroscopy without isolation. $^{13}C\{^1H\}$ NMR (labeled carbons only): δ 92.5 (t, J = 42.4 Hz), 73.0 (d, J = 43.2 Hz), 41.9 (J = 40.1). $^{31}P\{^1H\}$ NMR: δ 14.11 (s, J_{PtP} = 3324 Hz).

Reaction of 8a-3,4,5-$^{13}C_3$ with Et$_3$N. Triethylamine (15 μL, 0.11 mmol) was placed in an NMR tube containing a 4:1 mixture of **8a**-3,4,5-$^{13}C_3$ and **5a**-$^{13}C_3$ in $CDCl_3$ (0.60 mL) at 25 °C, and the resulting solution was analyzed immediately (∼3 min) by $^{13}C\{^1H\}$ NMR spectroscopy, which revealed the presence of **6a**-$^{13}C_3$ as the exclusive ^{13}C-labeled species present in solution.

Protodemetalation Experiments. *Reaction of **6a** with Benzyl-4-pentenylammonium Chloride.* Benzyl-4-pentenylamine (26.5 mg, 0.151 mmol) was added to a solution of **5a** (27 mg, 3.2 × 10^{-2} mmol) and $PhSiMe_3$ (1 μL, 6 × 10^{-3} mmol) in dioxane-d_8 (1.00 mL). ^1H NMR analysis of the resulting solution 5 min after mixing revealed complete consumption of **5a** to form azaplatinacyclobutane complex **6a** and benzyl-4-pentenylammonium chloride. The relative concentration of **6a** was determined by integrating the H_7 resonance of **6a** at δ 4.56 relative to the methyl resonance of $PhSiMe_3$ at δ 0.02. The solution was then heated to 120 °C for 16 h. ^1H NMR analysis of the resulting solution revealed formation of **2a** in 101 ± 5% yield by integrating the methyl doublet of **2a** at δ 1.21 relative to the methyl resonance of $PhSiMe_3$ at δ 0.02.

*Reaction of **6b** with Triethylammonium Tetrafluoroborate.* An NMR tube containing a solution of **6b** (20 mg, 2.7 × 10^{-2} mmol) and 1,3-dimethoxybenzene (1.38 mg, 1.0 × 10^{-2} mmol) in 15% dioxane/diglyme (v/v) was placed in the probe of an NMR spectrometer preheated at 78 °C. An initial ^1H NMR spectrum was acquired, the tube was ejected from the spectrometer, and $Et_3N{\cdot}HBF_4$ (5.7 mg, 3.0 × 10^{-2} mmol) was added to the tube. The solution was thoroughly mixed, and the tube was returned to the spectrometer for 12 h. ^1H NMR analysis of the resulting solution revealed formation of **2b** in 83% yield by integration of the pyrrolidine resonance of **2b** at δ 4.01 (d, 1 H) versus the methoxy resonance of 1,3-dimethoxybenzene at δ 3.81 (s, 6 H).

*Kinetics of the Reaction of **6b** with Triethylammonium Tetrafluoroborate.* A solution of **6b** (36.7 mg, 5.0 × 10^{-2} mmol, 65 mM) and $Et_3N{\cdot}HBF_4$ (70.9 mg, 0.375 mmol, 0.46 M) in d_8-dioxane/diglyme (1/5 v/v, total volume 0.75 mL at 75 °C) was placed into the probe of an NMR spectrometer preheated at 75 °C. The sample was allowed to equilibrate for 5 min and was then monitored periodically by ^{31}P NMR spectroscopy, analyzing the intensity of the phosphorus resonance of **6b** at δ 12.14. Data points (nt = 48) were acquired every 328 s for the first 2.8 h, every 698 s for the next 2.7 h, and every 1058 s thereafter. A plot of ln[**6b**] versus time was linear to ∼2.5 half-lives with a pseudo-first-order rate constant of k_{obs} = (9.37 ± 0.06) × 10^{-5} s^{-1} (Figure 6). Using a similar procedure, pseudo-first-order rate constants for the protodemetalation of **6b** with $Et_3N{\cdot}HBF_4$ at 75 °C were determined at $[Et_3N{\cdot}HBF_4]_0$ = 0.10 (k_{obs} = (6.7 ± 0.1) × 10^{-5} s^{-1}), 0.33 (k_{obs} = (9.4 ± 0.1) × 10^{-5} s^{-1}), and 0.64 M (k_{obs} = (1.31 ± 0.02) × 10^{-4} s^{-1}). A plot of k_{obs} versus $[HNEt_3BF_4]$ was linear with a significant nonzero intercept (Figure 7), from which the rate constants k_1 = (5.5 ± 0.1) × 10^{-5} s^{-1} and k_2 = (1.1 ± 0.2) × 10^{-4} M^{-1} s^{-1} were determined.

*Reaction of **5b** and **6b** with HCl.* Anhydrous HCl(g) was added to the headspace of an NMR tube (2.7 mL, 1 atm, 0.11 mmol) containing a solution of **6b** (20 mg, 2.7 × 10^{-2} mmol) in $CDCl_3$ (0.60 mL), and the tube was shaken vigorously. ^1H and ^{31}P NMR spectroscopic analysis within 5 min of mixing revealed complete consumption of **6b** with formation of **2b**·HCl and **3**, the latter as the exclusive phosphorus-containing species. The headspace of the tube was then flushed with N_2, and the solution was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 4.1 mg, 2.7 × 10^{-2} mmol). GC analysis of the resulting solution revealed formation of pyrrolidine **2b** in 101% yield (from **6b**). In a similar procedure, reaction of **5b** (10 mg, 0.13 × 10^{-2} mmol) with HCl (1 atm, 0.11 mmol) for 5 min formed **2b**·HCl and **3** as the exclusive products. Removal of HCl and treatment with DBU formed **2b** in 95% yield (from **5b**) by GC analysis.

Data for **2b**·HCl: ^1H NMR δ 9.58 (br s, 1 H), 7.65−7.80 (m, 5 H), 4.43 (dd, J = 4.6, 13.5 Hz, 1 H), 4.28 (dd, J = 4.6, 13.5 Hz, 1H), 3.71 (dd, J = 6.7, 12.0 Hz, 1H), 3.29−3.37 (m, 1 H), 2.67 (dd, J = 7.7, 12.1 Hz, 1 H), 1.90 (dd, J = 6.0, 13.3 Hz), 1.80 (t, J = 12 Hz, 1 H), 1.5−1.7 (m, 3 H), 1.45 (d, J = 6.4 Hz, 3 H), 1.1−1.4 (m, 7 H). Data for **3**: $^{31}P\{^1H\}$ NMR δ 7.20 (s, J_{PtP} = 5045 Hz).

Kinetics of Catalytic Hydroamination. A suspension of **3** (19.7 mg, 1.9 × 10^{-2} mmol, 16 mM; [Pt] = 32 mM) and *n*-hexadecane (40 μL, 0.14 mmol) in diglyme (1.0 mL) was heated to 120 °C for 5 min in a thermostated oil bath and then treated with **1b** (120 mg, 0.49 mmol, 0.42 M) to form an amber solution (total volume 1.16 mL). Aliquots (25 μL) were removed periodically and analyzed by GC to determine the concentration of **1b** as a function of time. The corresponding plot of [**1b**] versus time was linear through ∼2.5 half-lives with a pseudo-zeroth-order rate constant of k_{obs} = (1.99 ± 0.04) × 10^{-3} M s^{-1} (Figure 8). Employing a similar procedure, pseudo-zeroth-order rate constants for the disappearance of **1b** were determined at [Pt] = 11 (k_{obs} = (6.6 ± 0.2) × 10^{-5} M s^{-1}), 21 (k_{obs} = (1.46 ± 0.03) × 10^{-4} and (1.29 ± 0.04) × 10^{-4} M s^{-1}), and 43 mM ((3.3 ± 0.30) × 10^{-4} M s^{-1}). A plot of pseudo-zeroth-order rate constants versus platinum concentration was linear with a slope of k_1 = (97.5 ± 0.6) × 10^{-3} s^{-1} (Figure S2 in the Supporting Information), and a plot of ln(k_{obs}) versus ln[Pt] was linear with a slope of 1.14 ± 0.08 (Figure 9).

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.5b00821.

General methods, experimental and spectral data for isotopically labeled 4-pentenylamines, platinum complexes **4b**−**6b**, and isotopomers of **4a**−**6a**, kinetic plots, and scans of NMR spectra (PDF)

Crystallographic data for **6a**·$^1/_2CH_2Cl_2$ (CIF)

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Notes

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