Published in final edited form as:

Organometallics. 2012 October 8; 31(19): 6843–6850. doi:10.1021/om300671j.

Mechanistic Studies of Azaphilic versus Carbophilic Activation by Gold(I) in the Gold/Palladium Dual-Catalyzed Rearrangement of Alkenyl Vinyl Aziridines

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Abstract

A vinyl aziridine activation strategy cocatalyzed by palladium(0) and a gold(I) Lewis acid has been developed. This rearrangement installs a C–C and a C–N bond in one synthetic step to form pyrrolizidine and indolizidine products. Two proposed mechanistic roles for the gold cocatalyst were considered: (1) carbophilic gold catalysis or (2) azaphilic gold catalysis. Mechanistic studies support an azaphilic Lewis acid activation of the aziridine over a carbophilic Lewis acid activation of the alkene.

Introduction

Recent years have witnessed substantial progress in the development of a variety of dual-catalyzed reactions as a strategy to access unique reactivity and selectivity. However, significantly less is known about designing dual-catalyzed reactions as compared to their singly catalyzed counterparts,^{1–14} especially about strategies for avoiding potentially undesired redox reactions between the catalysts that may quench their catalytic activity.^{8b} Among these dual-catalytic reactions, there are several classes of distinct catalyst pairs: metal-metal,^{1–8} metal-metalloid,^{9,10} metal-organocatalyst,^{11–13} and organocatalyst-organocatalyst.¹⁴ Our approach for developing dual-metal-catalyzed reactions aims to combine the well-established Lewis acidic activity of Au(I)^{15–17} with a Lewis basic transition metal catalyst.¹⁸ We have previously demonstrated that combining the distinct reactivities of Au(I) and Pd(0) catalysts allows for new reactivity unavailable to single-metal systems.^{3,4,19} Herein, we describe a new Au(I) and Pd(0) dual-catalytic system for the rearrangement of alkene-tethered vinyl aziridines and provide insight into the mechanism of this dual-catalytic system.

We were inspired by recent reports of gold-catalyzed *hydroamination* reactions of olefins, which are proposed to proceed through carbophilic activation leading to alkylgold intermediates (Scheme 1a).²⁰ Toste and coworkers have supported the elementary step of carbophilic activation through the isolation of alkylgold intermediates in a gold-promoted hydroamination reaction.²¹ In Au-catalyzed hydroamination reactions, this C–Au σ -bond is often proposed to undergo subsequent protodeauration to form a C–H bond; however, the exact role of the Lewis acidic metal is a subject of ongoing investigation.²²

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Supporting Information. Full experimental details, characterization data for all new compounds, and computational parameters. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Mechanistically related to the hydroamination reaction, we envisioned a *carboamination* reaction²³ (Scheme 1b). We hypothesized that vinyl aziridine **1** could undergo a carbophilic gold-catalyzed cyclization similar to Toste's aminoauration of olefins with ureas²¹ and Bertrand's aminoauration of alkynes with tertiary amines (Scheme 1a).²⁴ The resulting vinyl aziridinium **3** would be electronically activated for oxidative addition by Pd(0) because of the enhanced leaving group ability of the ammonium.²⁵ An intramolecular gold/palladium cross-coupling reaction would afford pyrrolizidine **2** and regenerate both gold and palladium catalysts.

Herein, we report a Pd and Lewis acid cocatalyzed rearrangement of vinyl aziridines to form pyrrolizidine and indolizidine frameworks. These two classes of *N*-fused heterocycles are of interest because of their biological activity.^{26–29} Subsequent mechanistic experiments revealed that the mechanism analogous to hydroamination shown in Scheme 1 was *not* operative in the carboamination transformation; instead, the reaction proceeds through an azaphilic activation pathway, which is uncommon for Au(I).^{30–32}

Results and Discussion

To probe the conceptualized carboamination reactivity, we treated *gem*-diphenyl vinyl aziridine **1a** with 5 mol % (CAAC)AuCl/NaBARF and 2.5 mol % Pd₂dba₃ in CD₂Cl₂ at room temperature (Table 1). This reaction afforded carboamination product pyrrolizidine **2a** in 76% isolated yield. This reaction tolerated adamantyl (**2b**, 86%), cyclohexyl (**2c**, 56%), and cyclopentyl (**2d**, 51%) substitutions. However, a *gem*-dimethyl group substitution (**1f**) gave no reaction, presumably due to a reduced rate of cyclization from a diminished Thorpe-Ingold effect.³³ Methyl substitution at the internal position of the tethered alkene was tolerated (**2e**, 67%). Increasing the olefin tether length in diphenyl vinyl aziridine **1g** afforded indolizidine **2g** in good yield (74%) with an increased diastereomeric ratio (10:1).

Control experiments revealed that both Pd₂dba₃ and in situ-generated (CAAC)AuBARF were required for the observed dual-catalytic reactivity (Table 2). In contrast to our previous reports of Pd/Au cocatalyzed reactions,^{3,4} however, this reaction displayed a slow but nonzero background reaction with Pd₂dba₃ alone.

In order to probe the mechanism of this reaction, *Z* and *E* monodeuterated analogs of vinyl aziridine **1a** were subjected to the dual-catalytic rearrangement conditions (eqs 2 and 3). The *Z* diastereomer (**1a'**) generated only the 1,2-*trans* product **2a'**, and the *E* diastereomer of aziridine (**1a''**) provided exclusively the 1,2-*cis* diastereomer **2a''**.

(2)

(3)

This observed stereospecificity was inconsistent with a carbophilic activation mechanism (Scheme 1b), which would have resulted in the opposite diastereomer of each product at the deuterium-labeled carbon. In a carbophilic activation mechanism, the cationic gold catalyst could bind reversibly to the tethered olefin³⁴ and serve as a carbophilic Lewis acid (Scheme 2, complex **9**). The aziridine would then be primed for an intramolecular *anti* aminoauration to provide **10**,³⁵ an elementary step well-established for other amine nucleophiles with both Au(I)^{20a,21} and Au(III).³⁶ Pd(0) could then undergo oxidative addition into the aziridinium moiety, and alkyl Au- to- Pd alkyl transmetalation³⁷ with retention of configuration (Pathway A) would provide palladacycle **11**. A stereochemically retentive transmetalation, which is typical for with Pd(II) with relatively nonpolar organometallic complexes such as trialkyl-³⁸ and pinacol-boronates³⁹ and alkyl mercury(II) complexes,⁴⁰ is expected due to the nonpolar nature of the C–Au bond.⁴¹ A retentive C–C bond-forming reductive elimination⁴² from Pd(II) intermediate **11** would have provided the expected 1,2-*cis* product **2a'**. Instead, 1,2-*trans* pyrrolizidine product **2a''** was formed exclusively, thus eliminating Pathway A from further consideration.

This surprising mechanistic data inspired us to consider several alternative mechanisms (Scheme 2). First, Pd(0) could undergo oxidative addition into the aziridinium complex **10** but instead undergo an *invertive* transmetalation reaction (Pathway B). However, invertive transmetalation reactions generally occur only for polarized carbon–metal bonds,⁴³ such as alkyl lithium⁴⁴ and alkyl trifluoroborate⁴⁵ compounds or in highly polar solvents, such as HMPA.^{46,47} In contrast, the C–Au bond is largely nonpolar,⁴¹ and the dichloromethane used in our reactions is a less polar solvent; an invertive transmetalation from an alkyl-Au complex would thus represent an unusual elementary step. Pathway B was therefore unlikely, but further investigation into the stereochemistry of this fundamental step was warranted (*vide infra*).

We considered another possible mechanism in which the cationic gold complex bound reversibly to the aziridine nitrogen as an azaphilic Lewis acid^{30–32} (complex **9b**), priming the vinyl aziridine for oxidative addition by Pd(0)⁴⁸ to provide heterobimetallic amide **13**. Intermediate **13** is then poised for a *syn* aminoauration reaction (Pathway C), a selectivity postulated only very infrequently.^{49–52} The alkyl-Au fragment in **14** could then undergo a retentive transmetalation, which is expected based upon the polarity of the C–Au bond. Finally, retentive reductive elimination from palladacycle **12** would provide the observed diastereomer of pyrrolizidine product **2a''**. The dearth of evidence supporting *syn* aminoauration by Au(I) in contrast to the abundance of data supporting *anti* aminoauration by Au(I)^{20a,21} makes this mechanistic hypothesis less likely; however, this pathway cannot be disregarded.

A final possible mechanism was considered in which the Pd intermediate **15** undergoes a *syn* aminopalladation^{53,54} reaction with the tethered olefin to provide **12** directly (Pathway D). This mechanistic hypothesis circumvents the unlikely *syn* aminoauration step and avoids the stereochemical complexities associated with the alkyl Au-to-Pd transmetalation reaction. Pathway D bears a mechanistic resemblance to the Pd-only-catalyzed aminoarylations of

olefins pioneered by Wolfe, which have been shown to proceed through *syn* aminopalladation elementary steps.⁵⁵

In order to further differentiate between the four proposed mechanisms, we attempted to characterize several of the organometallic intermediates shown in Scheme 2, but these attempts were ultimately unfruitful. Attention was instead turned towards probing the stereochemical outcome of the possible Au-to-Pd alkyl transmetalation step. We prepared alkylgold complex **16** (Figure 1a), which was recently isolated by Toste in a gold-promoted mechanistic study of the aminoauration of olefins.²¹ We envisioned that this isolable complex could model the reactivity of possible catalytic intermediate **10** (Scheme 2, Pathways A and B) with Pd: both complexes possess an alkyl-Au fragment exocyclic to a pyrrolidine core. Furthermore, both also possess a tethered Lewis basic group (Figure 1a, highlighted in blue), which could serve as a directing group for transmetalation by first binding to Pd.

We treated model alkylgold complex **16** with a source of dicationic Pd and 2,2'-bipyridine. The sole pyrrolidine product was characterized spectroscopically as **17** via an nOe experiment. Specifically, irradiating at the indicated proton in complex **17** resulted in an nOe enhancement at the alkyl-Pd chiral center (Fig. 1b). Molecular modeling using density functional theory (DFT) calculations using the PBE functional⁵⁶ on the analogous perprotiated complex (Figure 2) confirm the urea binding mode shown in Figure 1b. This first example of a direct observation of the stereochemical outcome of a transmetalation of chiral sp^3 organogold to Pd indicates that the transmetalation from Au complex **16** occurs with complete retention of stereochemistry. Given the nOe data and the several prior reports of retentive transmetalation with other nonpolar organometallic compounds,^{38–40} mechanistic Pathway B (Scheme 2) was eliminated from further consideration. Thus, both carbophilic activation mechanisms A and B were ruled out on the basis of the experimental data.

With Pathways A and B eliminated from consideration in favor of azaphilic pathways C and D, we then sought to understand more about the nature of the active azaphilic Au(I) cocatalyst. The reaction of (CAAC)AuCl (**7**) with NaBARf (**8**) rapidly and quantitatively affords (CAAC)AuBARf and NaCl; however, it is possible that NaBARf was present in equilibrium⁵⁷ with (CAAC)AuBARf/NaCl and cocatalyzed the reaction. Indeed, even in the absence of Au(I), NaBARf was a competent cocatalyst with Pd(0), promoting the reaction in 87% ¹H NMR spectroscopic yield (Table 3, entry 1). This assay yield is higher than that which was obtained in the presence of (CAAC)AuBARf/NaCl (entry 2), yet rigorous removal of NaCl from (CAAC)AuBARf confirmed that (CAAC)AuBARf was a competent cocatalyst in the absence of Na (entry 3).⁵⁸

In order to separate the effects of the Na cation from the BARf anion, (NBu₄)BARf was examined as a cocatalyst with Pd(0) (entry 6). Its poor cocatalytic activity confirms the hypothesis that the azaphilic Lewis acid Na⁺ is indeed responsible for the observed reactivity from NaBARf rather than any significant ion exchange effects from the BARf anion itself, in contrast to that reported for a previous π -allyl palladium coupling.⁵⁹

We suspected that the same azaphilic activation mechanism may be operative for both (CAAC)AuBARf and NaBARf. To test this hypothesis, we repeated the rearrangement of deuterium-labeled aziridine **1a'** (eq 2) after rigorously removing NaCl from (CAAC)AuBARf. The 1,2-*trans* product **2a'** was again obtained, albeit with a longer reaction time (perhaps due to catalyst loss upon filtration); the stereochemical course of the reaction is thus the same for the Au(I) Lewis acid and the mixture of Au(I) and Na, suggesting that Na and Au(I) Lewis acids operate by a similar azaphilic activation pathway.

Therefore, the mechanism of this reaction represents an uncommon reaction manifold for Au(I), which is generally employed as a carbophilic Lewis acid.^{15–17} We have further supported the plausibility of this Au–N binding mode in the presence of a tethered olefin by DFT calculations, which revealed that the binding of a model (NHC)Au(I) cation to vinyl aziridine **1f** favored the N-bound complex³⁰ over the π -complex by nearly 17 kcal/mol (eq 4). Of course, these data do not preclude the possibility of a Curtin-Hammett-type reaction manifold in which the thermodynamically disfavored π -complex (**19**) is the kinetically competent intermediate; however, they do demonstrate the feasibility of Au(I) binding to the aziridine as originally established crystallographically by Nöh and coworkers,³⁰ and that this Nöh-type binding remains thermodynamically accessible even in the presence of a potentially competing olefin.

(4)

Based on the mechanistic data and the efficacy of the NaBARF Lewis acid as a cocatalyst, we propose the catalytic cycle shown in Scheme 3. First, the aziridine undergoes Lewis acid-promoted oxidative addition^{9–10} by Pd(0). The resulting Pd(II) intermediate **20** then undergoes a *syn* aminometallation.⁶⁰ The observed product **2** is then obtained following a reductive elimination from palladacyclic intermediate **21**. This catalytic cycle is generalized from mechanistic Pathways C or D from Scheme 2.

Conclusions

In conclusion, we have demonstrated a Pd and Lewis acid dual-catalyzed rearrangement of vinyl aziridines to pyrrolizidine and indolizidine products. This reaction installs a new C–C bond and a new C–N bond in *N*-fused heterocyclic frameworks in one synthetic step. During the course of mechanistic experiments, an alkyl Au/Pd transmetalation was found to occur with complete retention of stereochemistry. This first study of the retentive stereochemistry of transmetalation of chiral organogold(I) complexes to palladium and a successful strategy for avoiding competing redox quenching of gold(I) by palladium provide insight into this subset of dual-metal catalysis.^{8b,18}

The reaction was found *not* to proceed through carbophilic Au(I) catalysis. Instead, an uncommon role for catalytic Au(I) as an azaphilic Lewis acid was revealed, even in the presence of a potential competing carbophilic activation pathway. These mechanistic studies lend support to previous reports that gold binding to heteroatoms may be responsible for catalytic activity in some gold-catalyzed hydroamination reactions of alkenes, rather than direct gold π -complex activation.^{22a–c}

Experimental

General information

All chemicals were used as received from commercial sources unless otherwise noted. Acetonitrile, dichloromethane, diethyl ether, methanol, and tetrahydrofuran were dried by passage through an alumina column under argon pressure on a push-still solvent system.

Dichloromethane- d_2 was dried over CaH_2 , degassed using three freeze-pump-thaw cycles, and vacuum transferred prior to use. *N,N*-Diisopropyl ethyl amine (DIPEA) was distilled under nitrogen before use. Aziridines **1a–g** were prepared as described in the electronic Supplementary Information. $(\text{CAAC})\text{AuCl}^{61}$ (**5**) and NaBARF^{62} (**6**) were prepared according to literature procedures. $[\text{Pd}(\text{MeCN})_4][\text{BF}_4]_2$ was purchased from Sigma-Aldrich. All manipulations were conducted in a glovebox under nitrogen atmosphere or using standard Schlenk techniques unless otherwise specified. Analytical TLC was performed on Dynamic Absorbents 250 μm TLC plates with F-254 indicator. Plates were visualized under UV irradiation (254 nm), and/or using an aqueous solution of KMnO_4 or an ethanol solution of ninhydrin followed by heating. Flash chromatography was conducted using Grace Davisil 35–70 μm silica gel or Acros 50–200 μm basic aluminum oxide (activity I). All proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on a Bruker DRX-500 spectrometer, a Bruker DRX-500 spectrometer outfitted with a cryoprobe, or a Bruker AVANCE600 spectrometer. All chemical shifts are reported in parts per million. ^1H and ^{13}C NMR spectroscopy experiments are calibrated to the residual proteosolvent resonance. Low and high-resolution mass spectrometry data were obtained at a facility operated by the University of California, Irvine.

Diphenyl pyrrolizidine **2a**

In the glovebox, gold precatalyst **7** (3.0 mg, 0.020 mmol, 5.0 mol %), NaBARF salt **8** (4.4 mg, 0.020 mmol, 5.0 mol %), Pd_2dba_3 (2.3 mg, 0.010 mmol, 2.5 mol %), and aziridine **1a** (28.9 mg, 0.100 mmol, 1.00 equiv) were weighed into separate dram vials. Dry DCM (1.0 mL) was added via syringe to the dram vial containing $(\text{CAAC})\text{AuCl}$ and this solution was then added to the dram vial containing NaBARF . The $(\text{CAAC})\text{AuCl}/\text{NaBARF}$ solution was added to the dram vial containing aziridine **1a**. To the dram vial containing Pd_2dba_3 was added the solution containing substrate, $(\text{CAAC})\text{AuCl}$, and NaBARF in DCM. The dram vial was capped and allowed to stir for 24 h. The reaction was then taken out of the glovebox and purified by silica gel chromatography eluting using a gradient from 1:0:100 to 1:5:95 $\text{NH}_4\text{OH}:\text{MeOH}:\text{CHCl}_3$ to give **2a** as a white solid (22 mg, 76% yield, 1.0:1.0 d.r.). The isolation procedure did not alter the product d.r., which was detected as 1:1 by ^1H NMR spectroscopy in a separate reaction run in CD_2Cl_2 on 0.050 mmol scale. ^1H NMR (CDCl_3 , 500 MHz): δ 1.43–1.51 (m, 1H), 1.82–1.86 (m, 2H), 2.11 (dd, $J = 11.9, 10.6$ Hz, 1H), 2.19–2.23 (m, 2H), 2.42 (dd, $J = 11.1, 10.2$ Hz, 1H), 2.71–2.75 (m, 2H), 2.78–2.94 (m, 3H), 2.98 (dd, $J = 9.7, 3.5$ Hz, 2H), 3.07–3.17 (m, 1H), 3.38 (dd, $J = 8.6, 6.1$ Hz, 1H), 3.61–3.72 (m, 2H), 4.11–4.18 (m, 2H), 4.99–5.08 (m, 2H), 5.14 (app d, $J = 17.4$ Hz, 2H), 5.76–5.90 (m, 2H), 7.17–7.38 (m, 16H), 7.44–7.52 (m, 4H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 38.4, 39.3, 40.6, 45.2, 48.0, 55.9, 59.6, 60.8, 61.8, 62.9, 64.0, 66.2, 66.7, 114.6, 114.8, 126.0, 126.2, 126.6, 126.7, 126.9, 127.0, 128.1, 128.32, 128.34, 128.4, 139.2, 139.4, 146.3, 146.7, 147.4, 147.6. HRMS (ESI $^+$): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{N}$, 290.1909; found, 290.1911.

Adamantyl pyrrolizidine **2b**

In the glovebox, gold precatalyst **7** (6.3 mg, 0.010 mmol, 15 mol %) was dissolved in 0.3 mL dry DCM and added to a dram vial containing NaBARF salt **8** (9.2 mg, 0.010 mmol, 15 mol %). The resulting suspension was added to a screw-cap dram vial containing aziridine **1b** (18 mg, 0.069 mmol, 1.0 equiv). A single 0.3 mL portion of DCM was used to rinse the two vials formerly containing the gold precatalyst and the NaBARF salt to aid in complete transfer to the aziridine vial. Finally, Pd_2dba_3 (4.8 mg, 0.0052 mmol, 7.5 mol %) was added to the aziridine mixture as a solution in 0.3 mL DCM. The reaction vessel was capped and stirred at 25 $^\circ\text{C}$ in the glovebox 5 d. The crude reaction mixture was then removed from the glovebox and concentrated in vacuo. The mixture was purified using a silica gel pipet column eluting using a gradient 1:0:99 to 1:5:94 $\text{NH}_4\text{OH}:\text{MeOH}:\text{CHCl}_3$. The product was obtained as a mixture of diastereomers (16 mg, 88% yield, d.r. = 1.0 : 1.0). Diastereomer

A. ^1H NMR (CDCl_3 , 500 MHz): δ 1.69–1.99 (m, 14 H), 2.06 (dd, $J = 13.0$, 6.6 Hz), 2.59–2.64 (m, 1H), 2.85 ($J = 14.0$, 7.3 Hz, 1H), 3.20–3.26 (m, 1H), 3.29 (d, $J = 13.9$ Hz, 1H), 3.81 (t, $J = 10.0$ Hz, 1H), 4.02 (dd, $J = 12.1$, 6.7 Hz, 1H), 4.84 (d, $J = 13.7$ Hz, 1H), 5.03 (q, $J = 9.4$ Hz, 1H), 5.22 (d, $J = 10.3$ Hz, 1H), 5.28 (d, $J = 17.2$ Hz, 1H), 5.78–5.88 (m, 2H). Diastereomer B. 1.69–1.99 (m, 14 H), 2.12 (dd, $J = 13.8$, 6.5 Hz, 1H), 2.57 (d, $J = 8.4$ Hz, 1H), ca. 2.79 (dd, 1H), c.a. 3.31 (1H), 3.54–5.63 (m, 1H), 3.85 (d, $J = 13.6$ Hz, 1H), 4.06 (d, $J = 13.4$ Hz, 1H), 4.63 (dd, $J = 12.9$, 8.1 Hz, 1H), 5.08–5.14 (m, 1H), 5.17–5.25 (m, 2H), 5.70 (d, $J = 9.8$ Hz, 1H), 6.16 (d, $J = 9.9$ Hz, 1H). ^{13}C NMR (CDCl_3 , 125 MHz): 26.8, 26.9, 33.4, 33.4, 33.7, 35.0, 37.0, 39.4, 40.0, 42.6, 49.3, 68.4, 70.6, 72.4, 76.7, 119.3, 133.3. Note: Not all signals were observable. HRMS (GC/EI+): $[\text{M}]^+$ calcd for $\text{C}_{18}\text{H}_{27}\text{N}$, 257.2144; found, 257.2137.

Cyclohexyl spirocyclic pyrrolizidine 2c

In the glovebox, gold precatalyst **7** (6.7 mg, 0.011 mmol, 5.0 mol %) was dissolved in 0.3 mL dry DCM and added to a dram vial containing NaBARF salt **8** (9.7 mg, 0.011 mmol, 5.0 mol %). Two 0.3 mL portions of DCM were used as a rinse to ensure full transfer of the gold precatalyst to the NaBARF vial. The resulting suspension was added to a screw-cap dram vial containing aziridine **1c** (45 mg, 0.22 mmol, 1.0 equiv). Three 0.3 mL portions of DCM were used as a rinse to ensure full transfer of the (CAAC)AuCl/NaBARF suspension. Finally, Pd_2dba_3 (5.0 mg, 0.0055 mmol, 2.5 mol %) was added to the aziridine mixture as a solution in 0.3 mL DCM. Two 0.35 mL portions of DCM were used as a rinse to ensure full transfer of the Pd solution. The reaction vessel was capped and stirred at 25 °C in the glovebox for 48 h. The crude reaction mixture was then removed from the glovebox and concentrated in vacuo. The mixture was purified twice: once using a silica gel pipet column eluting from 1:5:94 $\text{NH}_4\text{OH}:\text{MeOH}:\text{CHCl}_3$ and then once using preparatory TLC developed using 1:10:89 $\text{NH}_4\text{OH}:\text{MeOH}:\text{CHCl}_3$. The product was obtained as a mixture of diastereomers (25 mg, 56% yield, d.r. = 2.6 : 1.0). Analytical purity was confirmed using GC/MS. Major diastereomer, ^1H NMR (CDCl_3 , 500 MHz): δ 1.26–1.98 (m, 10H), 2.06 (dd, $J = 13.5$, 6.0 Hz, 1H), 2.49–2.61 (m, 2H), 3.18–3.27 (m, 1H), 3.34 (d, $J = 13.5$ Hz), 3.78 (t, $J = 12.0$ Hz, 1H), 4.09 (dd, $J = 12.2$, 7.0 Hz, 1H), 4.44 (d, $J = 13.5$, 1H), 5.01–5.06 (m, 1H), 5.21–5.27 (m, 2H), 5.78–5.81 (m, 2H), 6.01 (d, $J = 10.0$ Hz, 1H). Minor diastereomer, ^1H NMR (CDCl_3 , 500 MHz): δ 1.26–1.98 (m, 10H), c.a. 2.06 (1H), 2.12 (d, $J = 7.4$ Hz, 1H), 2.45–2.49 (m, 1H), 2.76–2.83 (m, 1H), 3.53–3.58 (m, 1H), 3.69 (d, $J = 13.1$ Hz, 1H), 3.88 (d, $J = 13.0$ Hz, 1H), 4.66 (dd, $J = 12.5$, 7.4 Hz), 5.11–5.14 (m, 2H), 5.71–5.81 (m, 2H), 6.17 (d, $J = 10.1$ Hz). Note: The signal near 2.06 ppm is entirely obscured by the major diastereomer and was detected implicitly by over-integration of the peak. ^{13}C NMR (CDCl_3 , 125 MHz): 22.6, 23.1, 23.4, 23.6, 25.1, 25.3, 36.9, 36.9, 37.2, 37.4, 38.4, 40.1, 41.3, 43.6, 44.6, 67.5, 68.7, 68.9, 70.8, 74.5, 118.6, 119.2, 133.2, 134.9. Note: the signal at 74.5 ppm was only observable in an HMQC spectrum through its coupling to the corresponding *ipso* protons. Not all signals arising from the minor diastereomer were observable. HRMS (GC/EI+): $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_{23}\text{N}$, 205.1830; found, 205.1835. The relative stereochemistry of the major diastereomer of **2c** was determined through comparison of the ^1H NMR chemical shifts to the major diastereomer of **2d**.

Cyclopentyl spirocyclic pyrrolizidine 2d

In the glovebox, gold precatalyst **7** (9.2 mg, 0.015 mmol, 10. mol %) was dissolved in 0.3 mL dry DCM and added to a dram vial containing NaBARF salt **8** (13.3 mg, 0.0150 mmol, 10.0 mol %). Next, 0.3 mL of DCM was used as a rinse to ensure full transfer of the gold precatalyst to the NaBARF vial. The resulting suspension was added to a screw-cap dram vial containing aziridine **1d** (29.0 mg, 0.150 mmol, 1.00 equiv). Then, 0.3 mL of DCM was used as a rinse to ensure full transfer of the (CAAC)AuCl/NaBARF suspension. The resulting solution was added to a screw-cap dram vial containing Pd_2dba_3 (6.9 mg, 0.0075

mmol, 5.0 mol %). Then, 0.3 mL of DCM was used as a rinse to ensure full transfer of the Pd solution. The solution was transferred to a J. Young tube and 0.3 mL of DCM was used as a rinse to ensure full transfer of the solution. The solution was heated in the J. Young tube at 40 °C for 24 h. The crude reaction mixture was then concentrated in vacuo. The mixture was purified twice: once using a silica gel pipet column eluting with 0.1:1:10 NH₄OH:MeOH:CHCl₃ and then once using a silica gel pipet column eluting with 0.1:1:10 NH₄OH:MeOH:CH₂Cl₂. The product was obtained as a mixture of diastereomers (14.7 mg, 51 mol % d.r. = 4.4 : 1.0). The product was isolated with an inseparable 16% NH₄OH impurity. Major diastereomer. ¹H NMR (CD₂Cl₂, 500 MHz): δ 1.59–2.02 (m, 10H), 2.40 (dd, *J* = 13.0, 7.9 Hz, 1H), 2.59–2.66 (m, 1H), 3.19–3.26 (m, 1H), 3.46 (d, *J* = 13.0 Hz, 1H), 3.75 (t, *J* = 12.2 Hz, 1H), 3.90 (dd, *J* = 12.1, 6.5 Hz, 1H), 4.31 (d, *J* = 12.9, 1H), 4.81–4.87 (m, 1H), 5.21–5.25 (m, 1H), 5.27–5.32 (m, 1H), 5.82 (ddd, *J* = 17.2, 10.1, 7.4 Hz, 1H). ¹³C NMR (CD₂Cl₂, 125 MHz): δ 23.6, 25.3, 36.6, 36.7, 37.2, 40.3, 44.8, 49.6, 67.4, 73.0, 78.4, 118.8, 133.3. Minor diastereomer. ¹H NMR (CD₂Cl₂, 500 MHz): δ 1.59–1.98 (m, 10H), 2.56 (d, *J* = 13.4, 8.4 Hz, 1H), 2.69–2.75 (m, 1H), 3.33 (t, *J* = 12.3 Hz, 1H), c.a. 3.50 (m, 1H), 3.66 (d, *J* = 12.7 Hz, 1H), 3.97 (d, *J* = 12.7 Hz, 1H), 4.43 (dd, *J* = 12.2, 7.0 Hz, 1H), 4.98–5.06 (m, 1H), c.a. 5.20 (m, 1H), c.a. 5.28 (m, 1H), 5.76 (ddd, *J* = 17.4, 10.1, 6.8 Hz, 1H). ¹³C NMR (CD₂Cl₂, 125 MHz): δ 23.5, 24.5, 37.8, 38.7, 38.8, 41.8, 43.0, 66.6, 72.1, 78.8, 118.2, 134.3. One carbon signal arising from the minor diastereomer was not observable. LRMS (ESI⁺): [M+H]⁺ calcd for C₁₃H₂₂N, 192.17; found, 192.15. The relative stereochemistry of the major diastereomer was determined through NOESY analysis (the major diastereomer peaks in the ¹H NMR spectrum were assigned and then nOe enhancements were observed).

Cyclohexyl(methyl) pyrrolizidine 2e

In the glovebox, gold precatalyst **7** (3.6 mg, 0.0059 mmol, 10. mol %) was dissolved in 0.1 mL dry DCM and added to a dram vial containing NaBARF salt **8** (5.2 mg, 0.0059 mmol, 10. mol %). Next, 0.1 mL of DCM was used as a rinse to ensure full transfer of the gold precatalyst to the NaBARF vial. The resulting suspension was added to a screw-cap dram vial containing aziridine **1e** (13.0 mg, 0.0594 mmol, 1.00 equiv). Then, 0.1 mL of DCM was used as a rinse to ensure full transfer of the (CAAC)AuCl/NaBARF suspension. The resulting solution was added to a screw-cap dram vial containing Pd₂dba₃ (2.7 mg, 0.0030 mmol, 5.0 mol %). Then, 0.1 mL of DCM was used as a rinse to ensure full transfer of the Pd solution. The solution was transferred to a J. Young tube and 0.2 mL of DCM was used as a rinse to ensure full transfer of the solution. The solution was allowed to run in the J. Young tube at 25 °C for 48 h. The crude reaction mixture was then concentrated in vacuo. The mixture was purified twice, each time using a silica gel pipet column eluting from 1:5:95 NH₄OH:MeOH:CHCl₃. The product was obtained as a mixture of diastereomers (8.7 mg, 67 mol % d.r. = 2.3 : 1.0). Major diastereomer. ¹H NMR (CD₂Cl₂, 500 MHz): δ 1.26 (s, 3H), 1.35–1.71 (m, 12H), 1.82 (d, *J* = 13.5 Hz, 1H), 1.96 (ddd, *J* = 12.8, 8.2, 1.2 Hz, 1H), 2.39 (d, *J* = 9.5 Hz, 1H), 2.69 (dd, *J* = 11.8, 10.5 Hz, 1H), 2.86–2.93 (m, 1H), 2.92–3.0 (m, 1H), 3.08 (d, *J* = 9.4 Hz, 1H), 4.95 (ddd, *J* = 10.2, 1.8, 0.8 Hz, 1H), 5.04 (ddd, *J* = 17.1, 1.8, 1.1 Hz, 1H), 5.72 (ddd, *J* = 17.2, 9.9, 7.7 Hz, 1H). Minor diastereomer. ¹H NMR (CD₂Cl₂, 500 MHz): δ 1.20 (s, 3H), 2.40–2.50 (m, 2H), 3.32 (dd, *J* = 10.6, 8.0 Hz, 1H), 4.92 (ddd, *J* = 9.3, 1.8, 0.9 Hz, 1H), 5.02 (ddd, *J* = 17.1, 1.8, 1.2 Hz, 1H), 5.79 (ddd, *J* = 17.2, 9.9, 7.7 Hz, 1H). Some ¹H NMR signals overlapped with the ¹H NMR signals of the major diastereomer. ¹³C NMR (CDCl₃, 125 MHz): δ 23.2, 23.5, 24.3, 24.5, 26.3, 26.4, 30.2, 31.4, 36.4, 37.7, 39.0, 39.5, 41.3, 42.9, 45.7, 46.7, 49.1, 52.9, 58.9, 60.9, 66.8, 70.4, 113.9, 114.4, 140.3, 141.4. HRMS (ESI⁺): [M+H]⁺ calcd for C₁₅H₂₇N, 220.2065; found, 220.2058. The relative stereochemistry of the major diastereomer was determined through nOe analysis (the major diastereomer peaks in the ¹H NMR spectrum were assigned and then the proton at 1.26 ppm was irradiated and the nOe enhancements were observed).

Diphenyl indolizidine **2g**

In the glovebox, gold precatalyst **7** (1.5 mg, 0.0025 mmol, 5.0 mol %) was dissolved in 0.1 mL dry DCM and added to a dram vial containing NaBARF salt **8** (2.2 mg, 0.0025 mmol, 5.0 mol %). Next, 0.1 mL of DCM was used as a rinse to ensure full transfer of the gold precatalyst to the NaBARF vial. The resulting suspension was added to a screw-cap dram vial containing aziridine **1g** (15.2 mg, 0.0500 mmol, 1.00 equiv). Then, 0.1 mL of DCM was used as a rinse to ensure full transfer of the (CAAC)AuCl/NaBARF suspension. The resulting solution was added to a screw-cap dram vial containing Pd₂dba₃ (1.1 mg, 0.0013 mmol, 2.5 mol %). Then, 0.1 mL of DCM was used as a rinse to ensure full transfer of the Pd solution. The solution was transferred to a J. Young tube and 0.1 mL of DCM was used as a rinse to ensure full transfer of the solution. The solution was heated in the J. Young tube at 40 °C for 21 h. The crude reaction mixture was then concentrated in vacuo. The mixture was purified four times, each time using a silica gel pipet column eluting from 0.1:0.5:250 NH₄OH:MeOH:CH₂Cl₂. The product was obtained as a mixture of diastereomers (11.3 mg, 74% yield, d.r. = 10 : 1.0). Major diastereomer: ¹H NMR (CDCl₃, 500 MHz): δ 1.14–1.22 (m, 1H), 1.59–1.67 (m, 2H), 1.71–1.74 (m, 1H), 2.03–2.10 (m, 1H), 2.15 (dt, *J* = 13.1, 3.5 Hz, 1H), 2.27 (d, *J* = 11.6 Hz, 1H), 2.51 (dq, *J* = 13.2, 2.7 Hz, 1H), 2.79–2.89 (m, 1H), 3.25 (t, *J* = 8.3 Hz, 1H), 3.80 (dd, *J* = 11.7, 2.1 Hz, 1H), 4.90 (d, *J* = 10.4 Hz, 1H), 4.98 (d, *J* = 17.1 Hz, 1H), 5.75–5.83 (m, 1H), 7.14 (t, *J* = 7.2 Hz, 2H), 7.17–7.28 (m, 7H), 7.43 (d, *J* = 7.7 Hz, 2H). ¹³C NMR (CD₂Cl₂, 125 MHz): δ 28.0, 36.2, 37.7, 40.1, 46.6, 61.0, 62.2, 64.3, 113.2, 125.6, 126.1, 126.8, 128.2, 128.5, 128.9, 142.8, 147.4, 149.7. Minor diastereomer: ¹H NMR (CDCl₃, 500 MHz): δ 2.21 (d, *J* = 11.7 Hz, 1H), 2.38 (t, *J* = 8.6 Hz, 1H), 2.41–c.a. 2.51 (m, 1H), 2.63–2.68 (m, 1H), 2.89 (dd, *J* = 8.3, 1.8 Hz, 1H), 3.75 (dd, *J* = 12.0, 2.3 Hz, 1H), 5.87–5.95 (m, 1H). Other peaks overlap with the major diastereomer in the ¹H NMR spectrum. HRMS (ESI⁺): [M+H]⁺ calcd for C₂₂H₂₆N, 304.2065; found, 304.2060. The relative stereochemistry of the major diastereomer was determined through nOe analysis (the major diastereomer peaks in the ¹H NMR spectrum were assigned and then the proton at 2.79–2.98 ppm was irradiated and the nOe enhancements were observed).

Stereochemical investigation of transmetalation reaction of deuterio-labeled chiral alkyl gold complex **16**

Deuterium-labeled alkyl gold complex **16** was prepared from deuterated amine **S-14** according to the method described by Toste.²¹ The diastereomeric assignment described in the literature characterization was independently confirmed through nOe analysis.

In the glovebox, 2,2'-bipyridine (1.2 mg, 0.0080 mmol, 1.0 equiv) was dissolved in 0.2 mL CD₂Cl₂ and transferred to a dram vial containing [Pd(MeCN)₄][BF₄]₂ (4.9 mg, 0.0080 mmol, 1.0 equiv). The resulting yellow slurry was added to a dram vial containing alkyl gold complex **16** (6.4 mg, 0.0080 mmol, 1.0 equiv; 2:1 mixture of diastereomers at the deuterated position) using 0.3 mL CD₂Cl₂ as a rinse. The homogeneous reaction mixture was transferred to a J. Young tube for observation. Starting alkylgold complex **16** was slowly consumed over 16 h, and the sparingly soluble complex [Pd(MeCN)₄][BF₄]₂ entered solution as it reacted. After 16 h, all **16** had been consumed. In the glovebox, the brown, heterogeneous reaction mixture was filtered through a fiberglass pipet filter, and the NMR tube and filter were rinsed with dry DCM (2 × 1 mL) to ensure full transfer. The resulting brown solution was concentrated in vacuo. Further removal of volatiles under reduced pressure (< 10 mTorr) afforded a brown oily residue, which was removed from the glovebox for further purification. The sample was diluted with 0.5 mL DCM, and the addition of 1 mL Et₂O resulted in the formation of a dark brown precipitate, which was removed by filtration. The yellow filtrate was concentrated in vacuo to an oily yellow residue and diluted with a minimum of THF and loaded onto an Alltech 600 mg C₁₈ silica Luer-Lok silica cartridge. Elution with THF into 0.2 mL fractions afforded **17** as a mixture with a coproduct

containing the Ph₃PAu(I) fragment. The reaction was repeated on a larger scale (10×), but no further purification by precipitation or chromatography was possible. Spectroscopic characterization data were obtained from the mixture, with data for the major pyrrolidine product as follows. ¹H NMR (CD₂Cl₂, 500 MHz): δ c.a. 1.23 (0.66 H), 1.34 (s, 9H), 2.32 (dd, *J* = 12.2, 9.1 Hz, 1H), 2.79 (ddd, *J* = 12.2, 6.2, 2.1 Hz, 1H), c.a. 3.48–3.52 (1H), 3.53 (d, *J* = 10.8 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), complex overlapping peaks in the aromatic region. Note: The signals near 1.23 ppm, near 3.50, and in the aryl region are partially obfuscated. The minor deuterium diastereomer (0.33 H, arising from transmetalation of the minor diastereomer of deuterated alkylgold complex **16**) was not observable by ¹H or HSQC NMR spectroscopy, presumably because this signal overlaps with another peak. ¹³C NMR (CD₂Cl₂, 125 MHz): δ 20.1, 29.0, 46.9, 51.9, 56.3, complex aromatic region. Two-dimensional NMR techniques (COSY and HSQC, see Section VI) were instrumental in determining which ¹H and ¹³C signals arose from the transmetalation product **16**. HRMS (ESI⁺): [M]⁺ calcd for C₃₂H₃₄DN₄OPd, 598.1921; found, 598.1902. The observed isotope pattern matches the simulated pattern for **17**.

Control experiments

All control experiments were conducted according to the following general procedure, omitting one or more reagents as specified in Table 2 in the manuscript text. In the glovebox, into separate screw-cap dram vials were weighed vinyl aziridine **1a** (11.6 mg, 0.0400 mmol, 1.00 equiv), gold precatalyst **7** (1.2 mg, 0.0020 mmol, 5.0 mol %), NaBARf (**8**, 1.8 mg, 0.0020 mmol, 5.0 mol %), and Pd₂dba₃ (0.9 mg, 0.001 mmol, 2.5 mol %). Mesitylene (5.6 μL, 0.040 mmol, 1.0 equiv) was added to the vial containing aziridine **1a**, and the resulting mixture was dissolved in 0.2 mL CD₂Cl₂ and transferred successively to the dram vials containing gold precatalyst **7**, BARf salt **8**, and Pd₂dba₃ in that order. Each vial was rinsed successively with one 0.2 mL portion of CD₂Cl₂, and the reaction vessel was capped and allowed to sit in the glovebox for the indicated period of time. The crude reaction was then removed from the glovebox and transferred to an NMR tube for analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank for funding the NSF via a CAREER award (CHE-0748312) to S.A.B, the NIH (1R01GM098512-01A1), and the NSF for a Graduate Fellowship to J.J.H (NSF-201015893). We also thank the NSF for a grant supporting the UCI computational cluster (CHE-0840513). DFT calculations were performed with the assistance of Dr. Nathan R. M. Crawford. We also thank the University of California, Irvine for a Regents Dissertation Fellowship for Y. S. and for additional funding, as well as Mr. Michael D. Garrison and Ms. Eva M. Hahn for assistance with substrate synthesis.

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Figure 1.

(a) A possible catalytic intermediate (**10**) and its isolable model complex (**16**). (b) Stoichiometric alkyl transmetalation from Au to Pd showing complete retention of stereochemistry.

Figure 2.
Calculated structure of perprotiated **17** with counterion and aromatic protons omitted for clarity.

Previous work:

a) Carbophilic gold catalysis: A proposed pathway for hydroamination

This work:

b) Analogous mechanistic proposal: carbophilic carboamination (later revised)

Scheme 1.

(a) Illustrative example of proposed carbophilic hydroamination work by others. (b) This work: original envisioned analogous mechanism for carbophilic carboamination.

Scheme 2.
Possible mechanistic pathways explaining the stereochemical course of the reaction.

Scheme 3.
General catalytic cycle.

Table 1

Substrate scope of the dual-catalyzed carboamination reaction.

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="border: 1px solid black; padding: 10px; text-align: center;"> <p>$n = 0, 1$</p> <p>1 2</p> </div> <div style="text-align: center;"> <p>(CAAC)AuCl (7)</p> <p>NaB(CF₃)₄ (8)</p> </div> </div>			
Starting material	Product	Isolated Yield	d.r.
		76%	1:1
		86% ^a	1:1
		56% ^b	3:1
		51% ^{c,d}	4:1
		67% ^{b,c}	2:1
		NR ^c	-

Starting material	Product	Isolated Yield	d.r.
 1g	 2g	74% ^d	10:1

^a 15 mol % (CAAC)AuCl/NaBARf, 7.5 mol % Pd₂dba₃, 5 d.

^b 48 h.

^c 10 mol % (CAAC)AuCl/NaBARf, 5 mol % Pd₂dba₃.

^d 40 °C.

Table 2

Control experiments.

Catalyst(s)	Loading	Time	Conversion ^a
(CAAC)AuCl/NaBArF (7/8)	5.0 mol % / 5.0 mol %	15 h	No reaction
CAAC carbene/Pd ₂ dba ₃	10. mol % / 5.0 mol %	16 h	No reaction
PdCl ₂ (PPh ₃) ₂ /AgSbF ₆	10. mol % / 20. mol %	16 h	Decomposition
Pd ₂ dba ₃	5.0 mol %	15 h	7 %
NaBArF (8)	5.0 mol %	16 h	No reaction
CAAC carbene	10. mol %	16 h	No reaction

^aBy ¹H NMR spectroscopy.

Table 3

Investigation into the active Lewis acid cocatalyst from Table 1

Entry	Lewis Acid	¹ H NMR Yield ^a
1	NaBARF (8)	87%
2	(CAAC)AuBARF generated <i>in situ</i> from 7 + 8 , NaCl not removed	79%
3	(CAAC)AuBARF pre-formed from 7 + 8 , NaCl removed	64%
4	(NBu ₄)BARF	27%
5	None	18%

^a Relative to mesitylene internal standard. Reaction conditions: **1a** (1.0 equiv), Pd₂dba₃ (2.5 mol%), Lewis acid (5.0 mol%), CD₂Cl₂, 25 °C, 24 h.