Mechanistic Study of Gold(I) Catalyzed Hydroamination of Allenes

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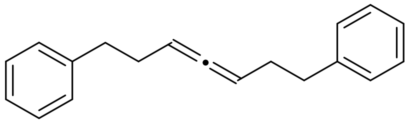
Supporting Information

I. General Procedures and Materials

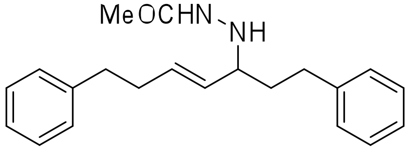
All reagents and solvents were obtained from commercial suppliers and used without further purification, unless otherwise specified. All air-sensitive reactions were carried out in dried glassware and solvent, under positive N_2 pressure using syringe and cannula techniques. Glassware was dried at 160 °C overnight or flame dried under vacuum immediately prior to use. Dry tetrahydrofuran was passed through a column of activated alumina. Following workup procedures, organics were concentrated under reduced pressure with a rotary evaporator. All flash chromatography was performed on Merck 60 silica gel (32-63 μm). Thin-layer chromatography (TLC) analysis was performed using Merck silica gel 60 F254 TLC plates, and visualized by staining with I_2, UV, anisaldehyde, and/or potassium permanganate. $Ph_3PAuNTf_2$ was prepared by the method described by Gagosz[1] and stored at -20 °C, protected from ambient light.

^1H and ^{13}C NMR spectra were recorded with Bruker AVQ-400, DRX-500, AV-500 and AV-600 spectrometers and chemical shifts are reported in ppm, relative to residual proton peaks of $CDCl_3$, CD_2Cl_2 or CD_3NO_2, unless otherwise noted. Deuterated solvents were obtained from Cambridge Isotope Laboratories and used without further purification. Enantiomeric excess was determined on a Shimadzu VP Series Chiral HPLC, using the Chiral PAK OD-H, eluting with a flowrate of 0.5 mL/min. Mass spectral and analytical data were obtained via the Micro-Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley.

II. Experimental



1,7-diphenylhepta-3,4-diene. To a dried flask containing a solution of Ph_3P (3.43 g, 13.1 mmol) in 40 mL dry THF, DIAD (2.75 mL, 13.1 mmol) was added dropwise under N_2 at 0 °C. The solution was stirred for 10 min at 0 °C before 1,7-diphenylhept-4-yn-3-ol[2] (1.73 g, 6.55 mmol) was added as a solution in 1 mL THF. After 45 min, 2-nitrobenzenesulfonohydrazide (2.82 g, 13.1 mmol) was added as slurry in 4 mL THF. The reaction was allowed to warm to 23 °C and was stirred for an 8 h, after which the crude reaction mixture was concentrated. The resulting viscous oil was passed through a silica plug, eluting with 300 mL of 12:88 EtOAc:hexanes. The organics were concentrated in vacuo and chromatographed on SiO_2, eluting with 0.5:99.5 EtOAc:hexanes. The allene product was isolated as a clear oil (660 mg, 41% yield). ^1H NMR spectra of the allene matches known spectroscopic data.[3]



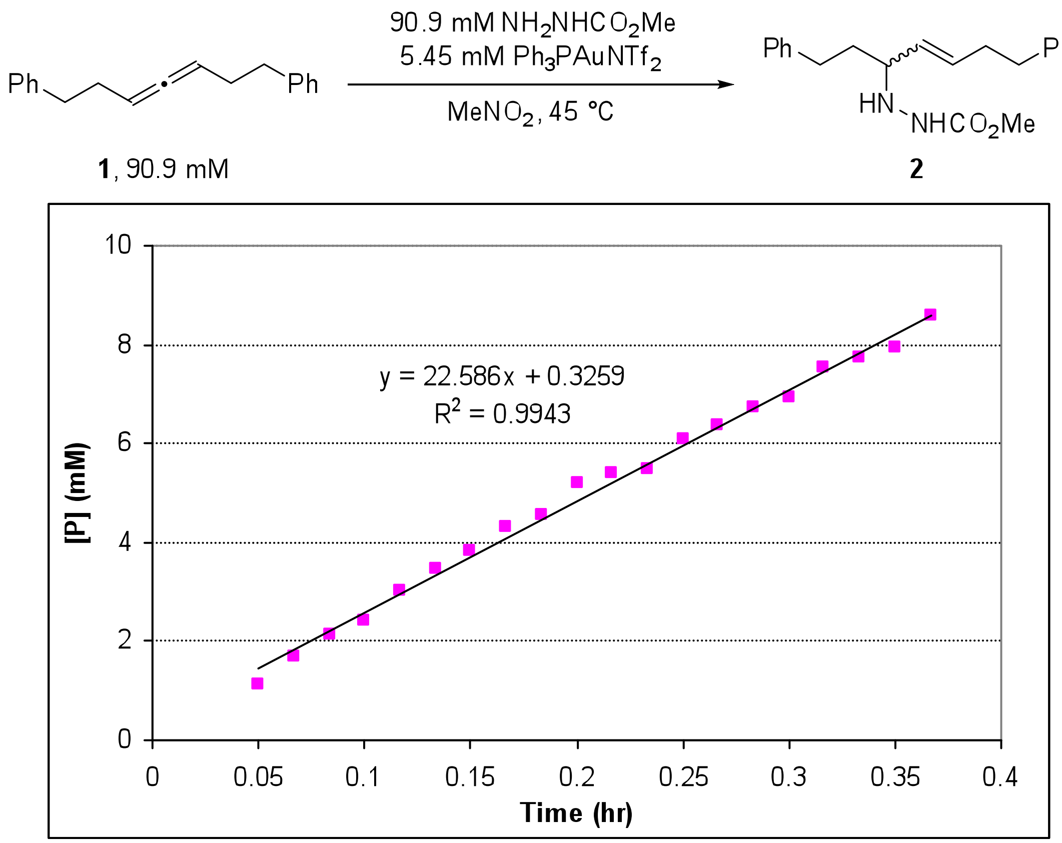
(E)-N'-(1,7-diphenylhept-4-en-3-yl)methyl carbazate (**2**). To a solution of 1,7-diphenylhepta-3,4-diene (**1**) (30.0 mg, 0.121 mmol) and methyl carbazate (27.2 mg, 0.302 mmol) in $MeNO_2$ (0.6 mL), $Ph_3PAuNTf_2$ (5.37 mg, 0.00726 mmol) was added. The reaction mixture protected from light, heated to 45 °C and stirred for 12 h. The crude reaction mixture was passed through a silica pad, eluting with 10 mL of 1:1 EtOAc:hexanes. The resulting solution was concentrated and chromatographed on SiO_2, eluting with 1:4 EtOAc:hexanes, to afford the product as a white solid (34 mg, 84%). ^1H NMR ($CDCl_3$, 600 MHz): δ 1.61-1.66 (m, 1 H), 1.81-1.85 (m, 1 H), 2.40-2.45 (m, 2 H), 2.51-2.63 (m, 2 H), 2.73-2.76 (m, 2 H), 3.36 (br s, 1 H), 3.73 (s, 3 H), 5.20-5.25 (dd, 1 H, *J* = 18, 10.2 Hz), 5.63-5.69 (dt, 1 H, *J* = 18, 8.4 Hz). $^{31}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 31.98, 34.13, 34.65, 35.56, 52.40, 62.87, 125.80, 125.92, 128.34, 128.54, 134.39, 141.54, 141.95, 157.74. HRMS (ESI) calculated for $[C_{21}H_{26}O_2N_2+Na]^+$: *m/z* 361.1886, found 361.1883.

*Kinetic Analysis of Formation of **2** from **1** and Methyl Carbazate.*

General Procedure for Kinetic Experiments. Kinetic experiments were performed using NMR techniques on a Bruker AV-600 spectrometer and reported rate constant represents an individual kinetics experiment. Standard solutions of catalyst were made by weighing the gold(I) complex into a vial and adding deuterated solvent. Stock solutions containing both 1,7-diphenylhepta-3,4-diene (**1**) and 1,3,5-tri-tert-butylbenzene (internal standard) were prepared similarly. To a J-Young tube protected from light, methyl carbazate, substrate, internal standard, and Au catalyst were added. The reactions were heated to 45 ºC and monitored by single pulse ^1H and $^{31}P\{^1H\}$ NMR. The concentrations of substrate and product were determined by relative integration to the t-butyl peak in the standard. The average rate constants reported reflect an average of three kinetic runs. The observed first order rate constant (k_{obs}) reported reflects $k_{obs} = (k_{trans} + k_{cis})$, where k_{trans} and k_{cis} correspond to the rate of formation for the trans and cis olefin products, respectively.

Order in Nucleophile. The order in nucleophile was determined by the method of initial rates at various concentrations of methyl carbazate. Following the general procedure for kinetics, 0.3mL of a standard solution of allene (12.4 mg, 50.0 mmol, per aliquot) and 1,3,5-tri-tert-butyl benzene (4.11 mg, 0.0167 mmol, per aliquot) in CD_3NO_2, 0.15 mL of a standard solution of methyl carbazate (4.50 to 14.64 mg, 50.0 to 163 mmol, per aliquot) in CD_3NO_2 and 0.1 mL of a standard solution of $Ph_3PAuNTf_2$ (2,22 mg, 3.00 mmol, per aliquot) in CD_3NO_2 were combined. The reaction was heated to 45 °C in probe and was monitored for conversion up to 9% by single pulse ^{1}H NMR. A representative plot of [**2**] (mM) versus time (h) is shown below with slope = 22.6 ± 0.4 mM h^{-1} and R^2=0.9943 (Figure S1).

Figure S1. A plot of [**2**] versus time at [Nuc] = 90.9 mM.

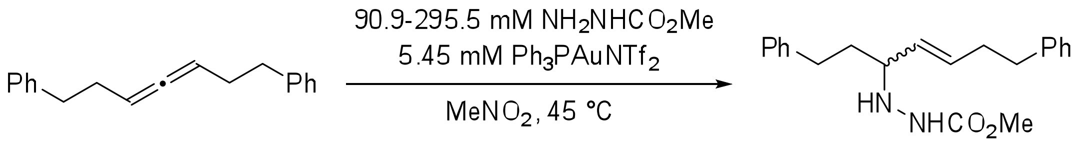


Kinetic data for k$_{obs}$ (where k$_{obs}$ ≈ (Δ[**2**]/Δt)/[**1**]$_0$ and [**1**]$_0$ = 90.91 mM) at all methyl carbazate concentrations are tabulated in Table S1. A plot of the data provided a straight line with R^2 = 0.9923 and slope = -1.47(9) x 10^{-4} ± h^{-1}, suggesting a zero order dependence on nucleophile (Figure S2). A non-linear least squares fit of the data to the equation f(x) = *a*(x)^n provided n = -0.1083 with R^2 = 0.9835 (Figure S3).

Table S1. Measured k$_{obs}$ at 90.9 to 295.5 mM of methyl carbazate.

[Nuc] (mM)	Trial 1 (h^{-1})	Trial 2 (h^{-1})	Trial 3 (h^{-1})	Average (h^{-1})
90.91	0.255(18)	0.242(4)	0.248(4)	0.248(7)
159.1	0.240(4)	0.238(3)	0.234(4)	0.237(3)
227.3	0.222(3)	0.229(3)	0.228(3)	0.225(2)
295.5	0.215(4)	0.218(3)	0.223(5)	0.214(1)

Figure S2. A plot of k_{obs} at various concentrations of methyl carbazate.



1, 90.9 mM

2

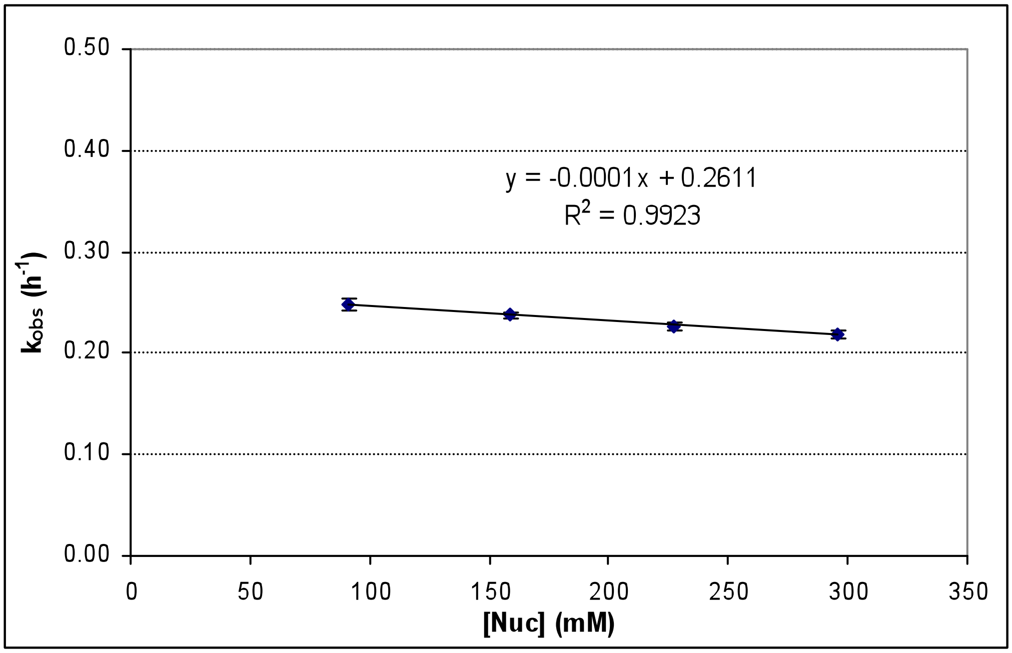
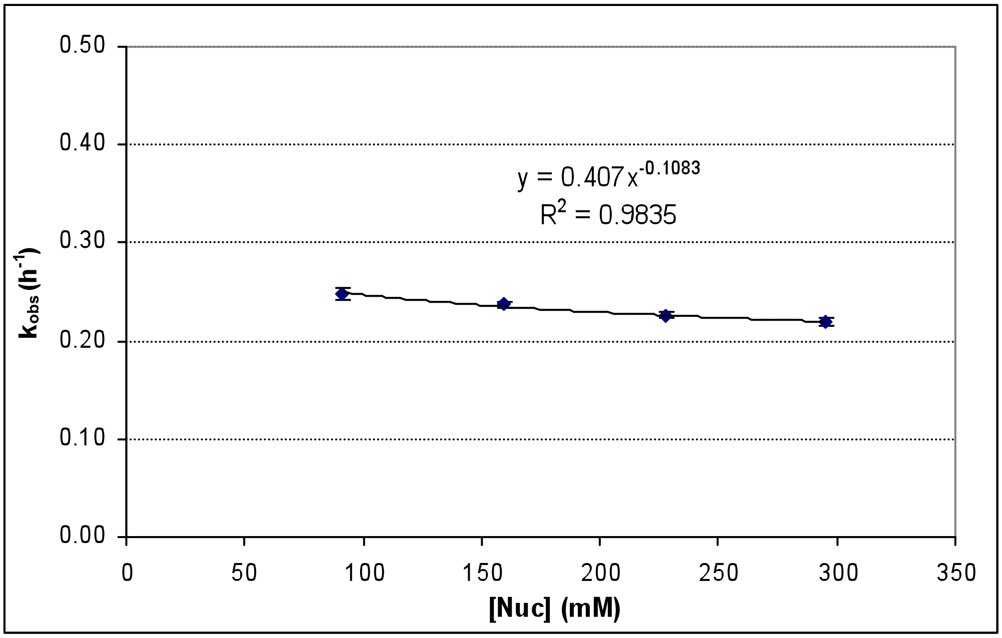
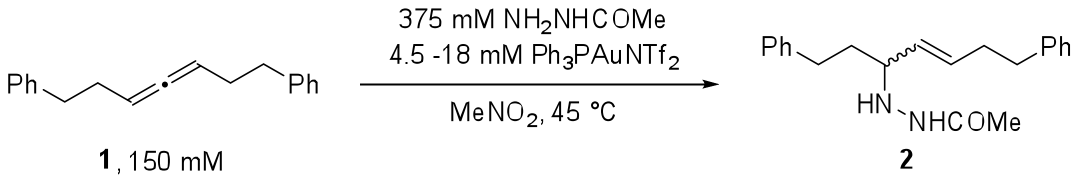


Figure S3. Non-linear least squares fit of the data to the equation f(x) = $a(x)^n$.



Order in Allene. The order in $Ph_3PAuNTf_2$ was determined by monitoring the rate of disappearance of allene at 3 to 12 mol % catalyst loadings. General procedure for kinetics was used with methyl carbazate (20.3 mg, 225 mmol), 0.4 mL of a standard solution containing (per aliquot) **1** (22.4 mg, 90.0 mmol) and 1,3,5-tri-tert-butylbenzene (7.40 mg, 30.0 mmol) (internal standard) in CD_3NO_2, and 0.2 mL of a standard solution containing (per aliquot) $Ph_3PAuNTf_2$ (2.00 to 7.98 mg, 2.7 to 10.8mmol) in CD_3NO_2. The reactions were heated to 45 ºC and monitored by single pulse ^{1}H NMR up to 80-85% conversion. Representative plots of –ln([**1**]$_t$/[**1**]$_0$) vs. time at 3, 6, 9 and 12 mol% catalyst loading is shown below (Figure S4). While the slope of the lines varies with catalyst loading, the plots are linear at all catalyst concentrations examined. This suggests that the reaction is first order in allene. This was confirmed by fitting the data to a least squares fit to *f*(x) = a(x)^n (Figure S5).

Figure S4. Plot of –ln([**1**]$_t$/[**1**]$_0$) versus time (h) at 3 to 12 mol% catalyst loading.



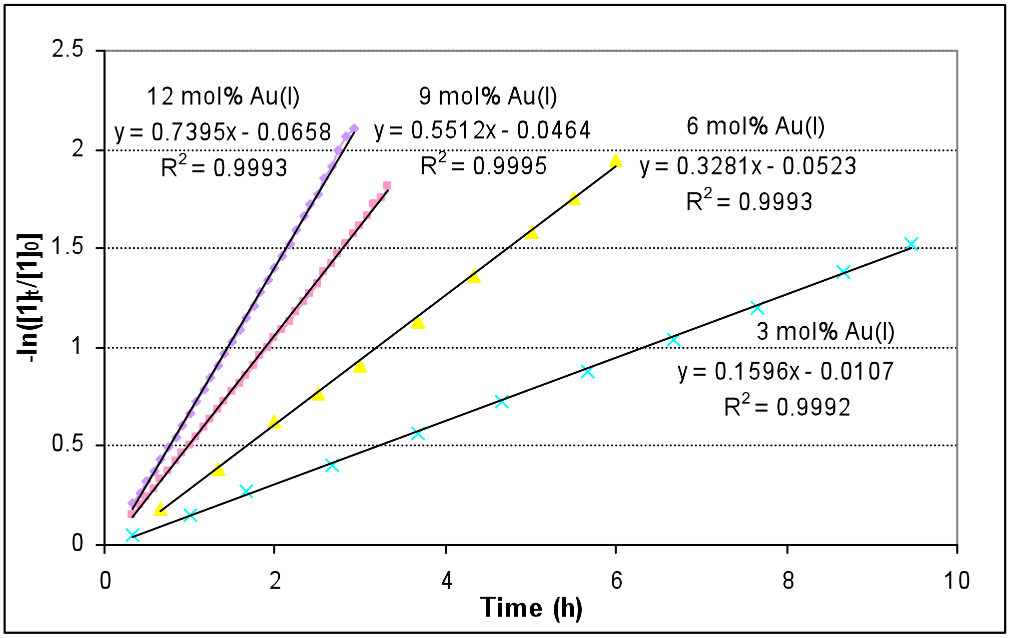
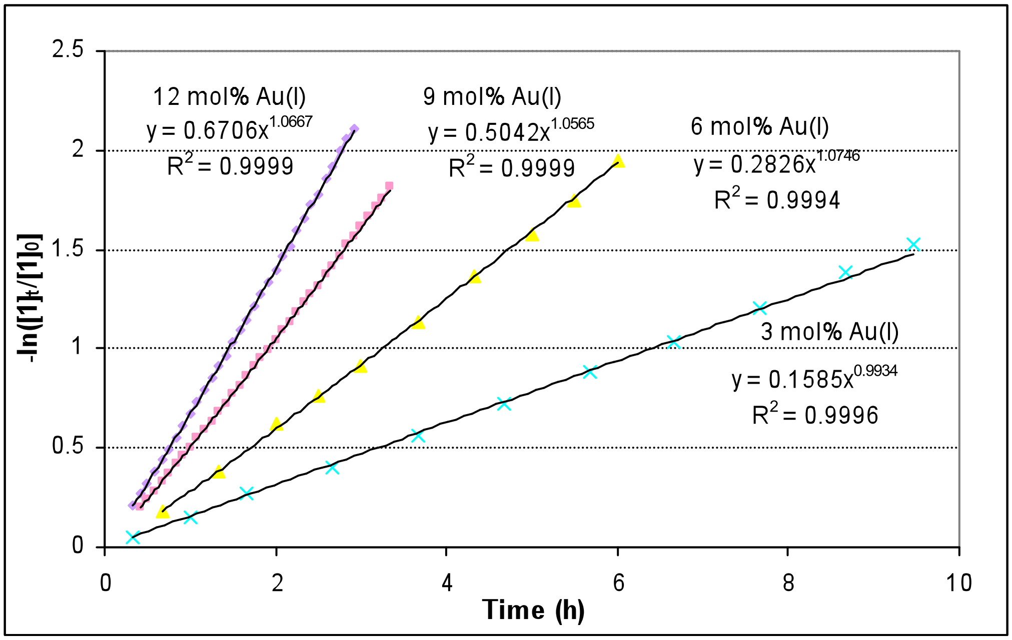


Figure S5. Non-linear least squares fit of the kinetics data to *f*(x) = a(x)^n .



Order in Catalyst. Each rate constant (k_{obs}) is obtained from the slope of the ln([**1**]$_t$/[**1**]$_0$) versus time plot at 3, 6, 9 and 12 mol% catalyst loading. Three independent kinetic experiments were averaged to obtain an average k_{obs}. The results are tabulated in Table 2. A plot of average k_{obs} versus [$Ph_3PAuNTf_2$] provided a straight line with slope = 0.0423(8), $R^2 = 0.9993$, suggesting a 1st order dependence on $Ph_3PAuNTf_2$ (Figure S6). This was confirmed by an non-linear least squares of the data to the equation $f(x) = a(x)^n$ which provided $n = 1.093$, with $R^2 = 0.9997$ (Figure S7).

Table 2. Measured rate constants at 3 to 12 mol% catalyst loading.

[PPh_3AuNTf_2] (mM)	Trial 1 (h^{-1})	Trial 2 (h^{-1})	Trial 3 (h^{-1})	Average (h^{-1})
4.5	0.175(4)	0.147(2)	0.160(2)	0.161(14)
9.0	0.368(11)	0.311(6)	0.328(3)	0.336(29)
13.5	0.534(17)	0.520(2)	0.551(2)	0.535(15)
18.0	0.718(24)	0.726(4)	0.740(4)	0.728(11)

Figure S6. Plot of average k_{obs} versus [$Ph_3PAuNTf_2$].

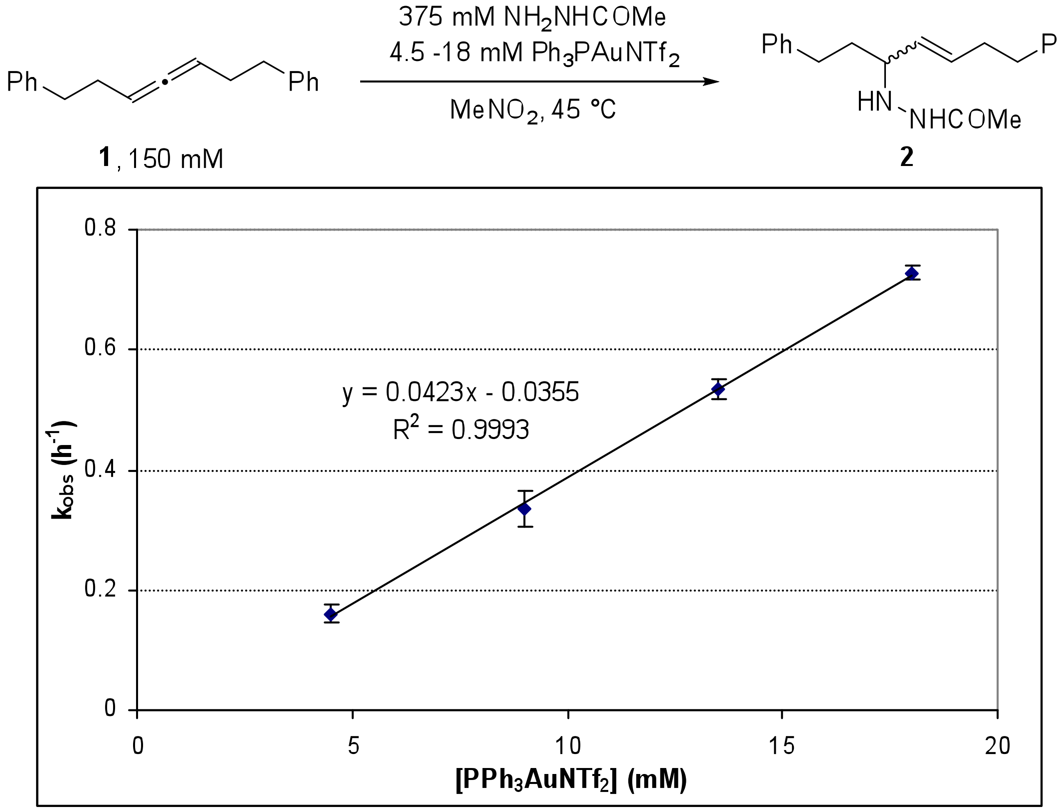
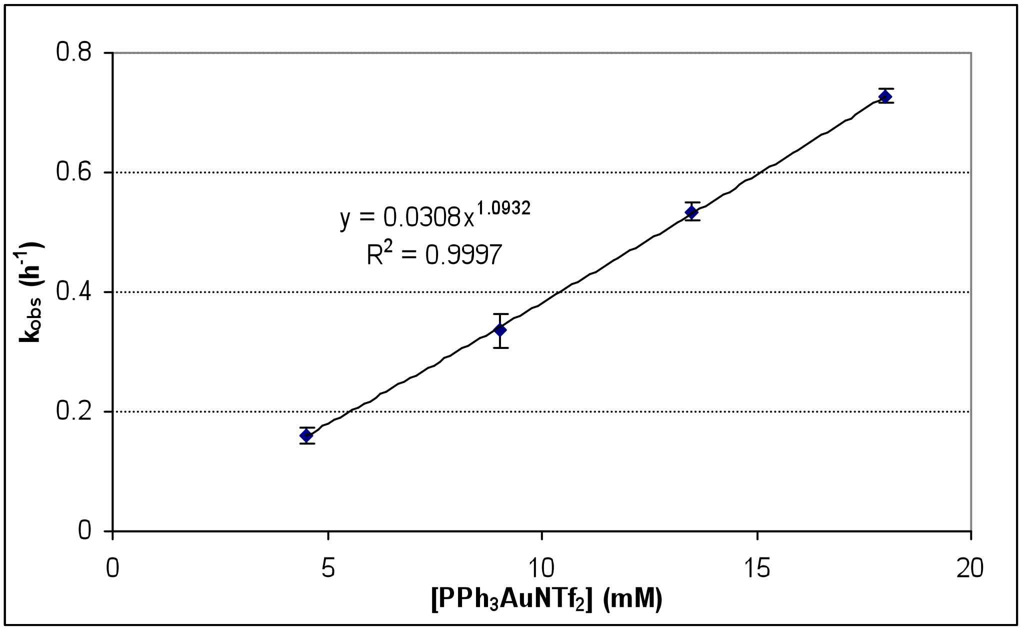
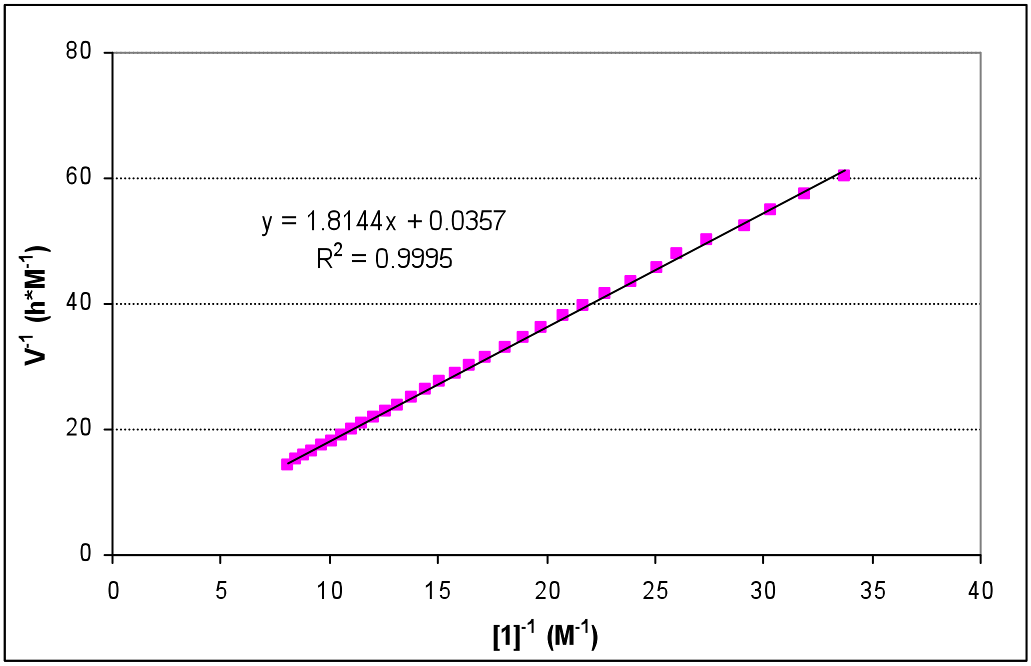


Figure S7. Non-linear least squares fit of the kinetic data to the equation $f(x) = a(x)^n$.



Calculation of K_M. A plot of [**1**] vs time was fitted to an exponential curve. The first derivative of this curve provided the instantaneous rate (V) at various [**1**]. The Michaelis-Mentent constant was found from the x-intercept of a double reciprocal plot of V^{-1} vs. $[\mathbf{1}]^{-1}$. A representative plot is shown below (Figure S8). This analysis was repeated for 5 independent kinetic runs at various concentrations of catalyst and the K_M reported is an average of these runs.

Figure S8. A representative Lineweaver-Burke plot of V^{-1} vs. $[\mathbf{1}]^{-1}$. For this example, methyl carbazate (0.5 mM), **1** (200 mM), and $Ph_3PAuNTf_2$ (10mM) was used.



<u>*Observation of catalyst resting state*</u>.

General procedure for kinetics was used with methyl carbazate (27.2 mg, 301.8 mmol), **1** (30.0 mg, 120.7 mmol), 1,3,5-tri-tert-butylbenzene (internal standard) (9.20 mg, 40.2 mmol), and $Ph_3PAuNTf_2$ (4.50 mg, 6.04 mmol) in 600 µL CD_3NO_2. The catalyst resting state was determined by monitoring ^{31}P NMR at 45 °C. Ten minutes after the addition of $Ph_3PAuNTf_2$ to the substrate mixture, the ^{31}P peak corresponding to the parent catalyst vanished and a new peak at $\delta = 45.2$ ppm (44.8 ppm in CD_2Cl_2) was observed. This peak persisted through the entire course of the reaction until the concentration of **1** was comparable to the concentration of $Ph_3PAuNTf_2$. Figure S9 is a ^{31}P NMR of the reaction from 11-95% conversion.

Figure S9. Monitoring the hydroamination reaction by ^{31}P NMR.

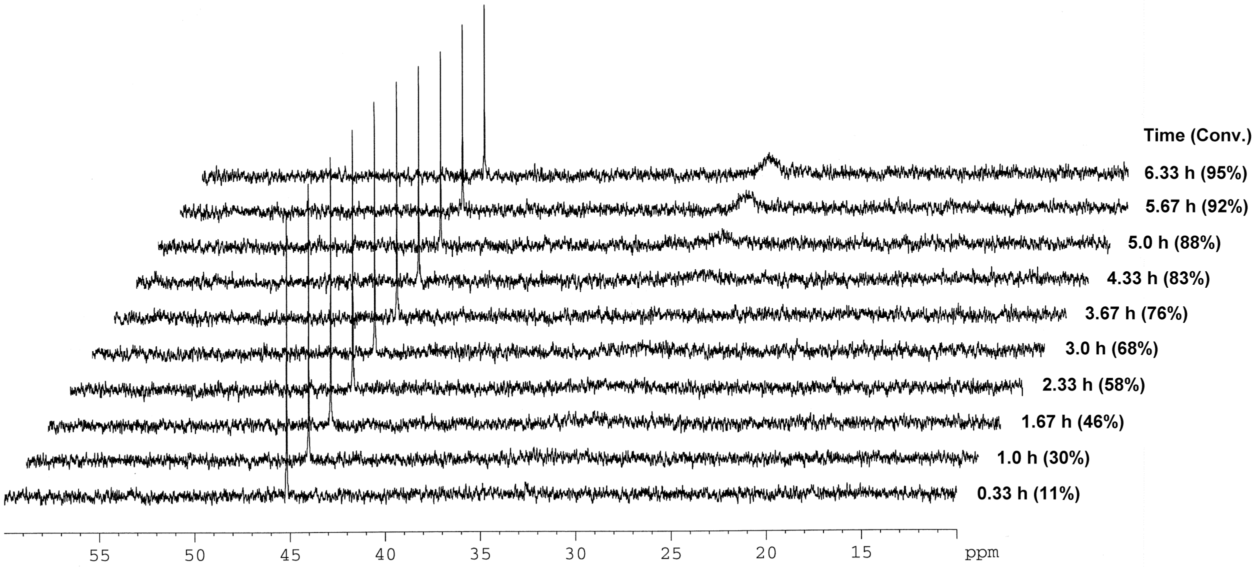


Figure S10 is a ^{31}P NMR reference spectra of Ph$_3$PAuNTf$_2$ in CD$_3$NO$_2$. Figure S11 is a ^{31}P NMR spectra of Ph$_3$PAuNTf$_2$ (10 mg, 13.5 mol) and methyl carbazate (1.2 mg, 13.5 mmol) in a 1:1 ratio in 500 μL. This solution produced a peak at $\delta = 29.7$ ppm that was distinct from that of the parent catalyst but was not that of the resting state. We assigned this peak as the gold-hydrazide complex, **4**.

Figure S10. Reference spectrum for the parent catalyst, Ph$_3$PAuNTF$_2$.

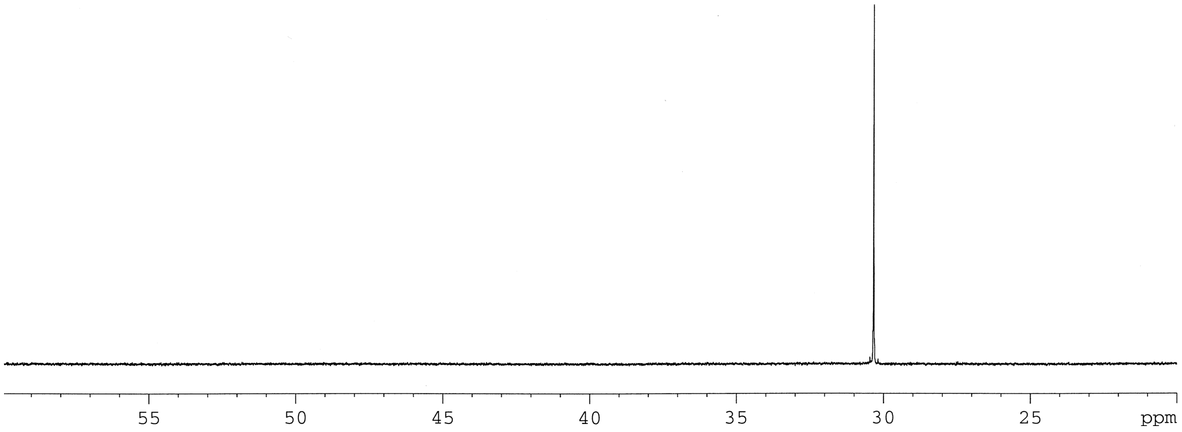


Figure S11. Solution of methyl carbazate and Ph$_3$PAuNTf$_2$ at 45 °C.

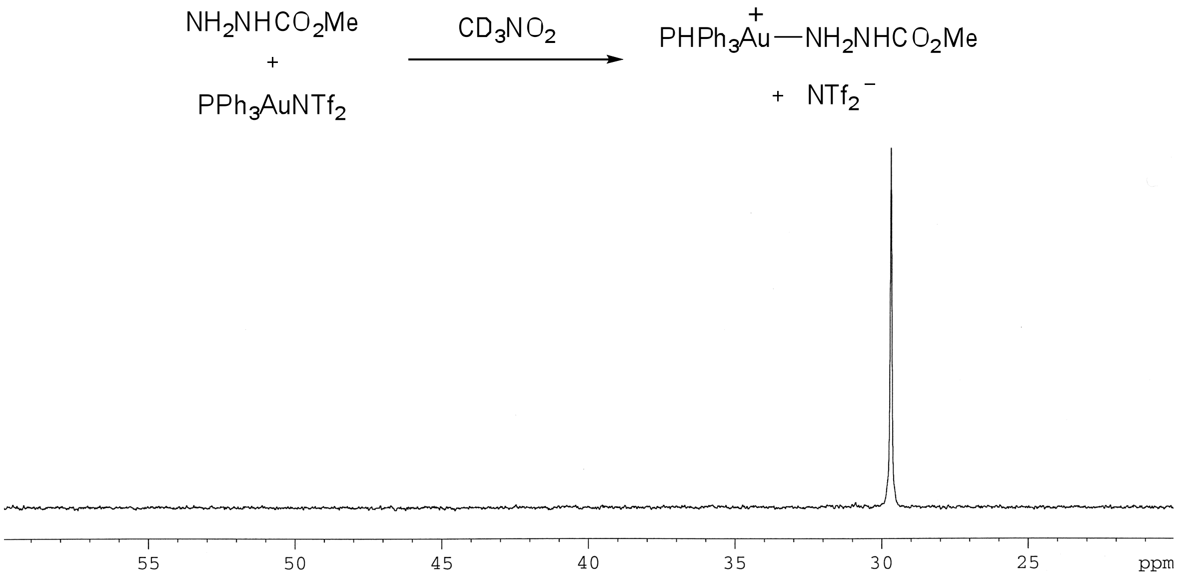
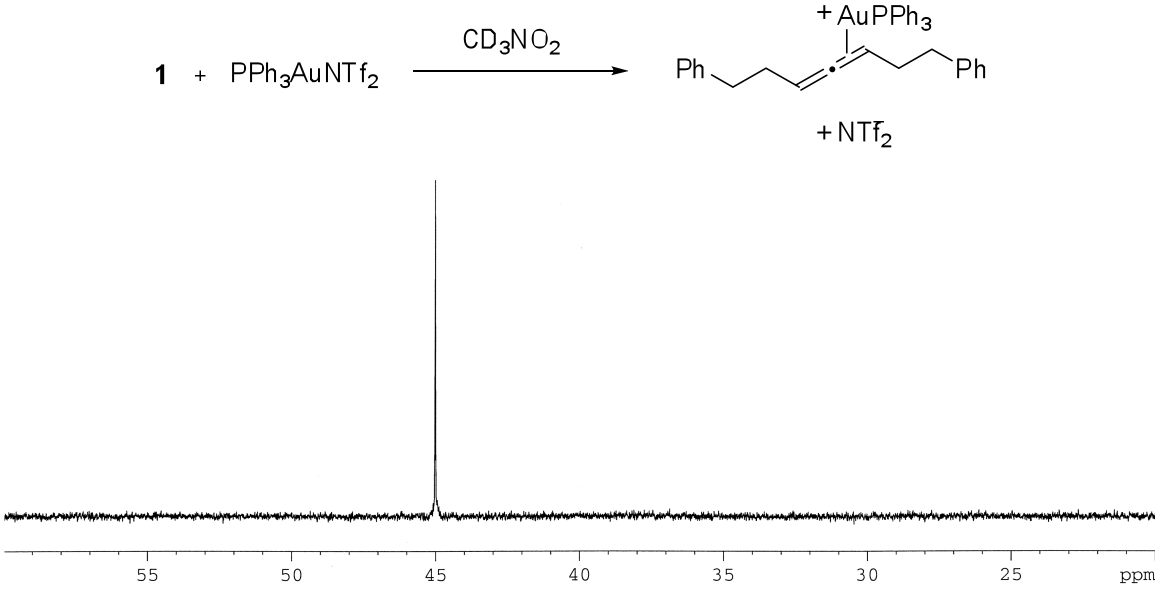


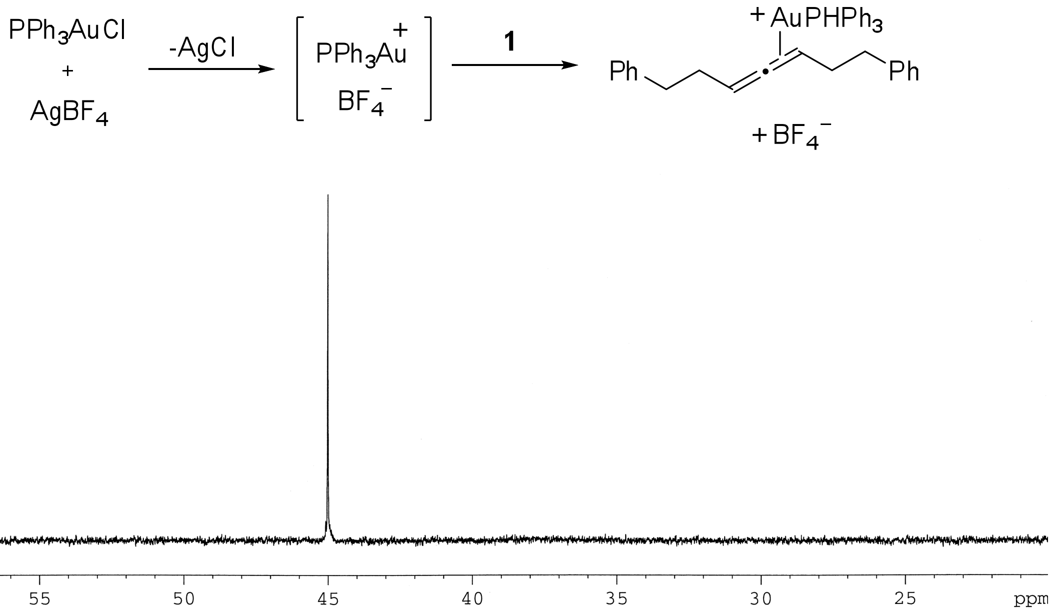
Figure S12 is a ^{31}P NMR spectra of Ph$_3$PAuNTf$_2$ (6.0 mg, 8.12 μmol) and **1** (20.2 mg, 81.2 mmol) in 400 μL CD$_3$NO$_2$. The reaction turned yellow upon addition of the allene. In the absence of any nucleophile, this mixture showed ^{31}P NMR resonance at 45.2 ppm (44.8 ppm in CD$_2$Cl$_2$), which resembled that of the resting state in the catalytic cycle, suggesting that the resting state of the catalyst was an allene-gold complex.

Figure S12. The gold-allene complex, generated from Ph$_3$PAuNTf and **1**.



This complex was also independently generated from Ph_3PAuCl (6.0 mg, 20.1 μmol), $AgBF_4$ (11.7 mmol, 60.2 μmol) and 1,7-diphenylhepta-3,4-diene (15.0 mg, 60.4 μmol). Gold chloride was combined with the silver salt and sonicated for 2 minutes in 700 μL CD_2Cl_2. The mixture was filtered through a micropipette filter fiber and added directly to **1**. The ^{31}P NMR spectra of the resulting solution showed the allene-gold complex (**4**) at δ 45.2 ppm (Figure S13).

Figure S13. The gold-allene complex, generated from Ph_3PAuCl, $AgBF_4$ and **1**.

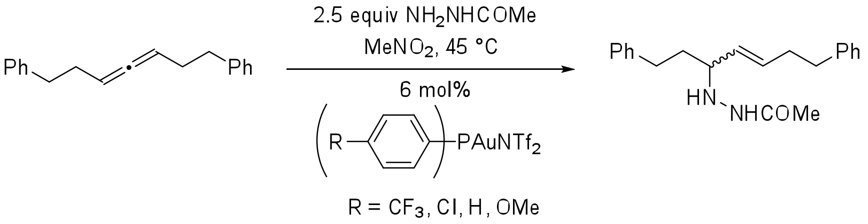


In order to verify the NMR assignments, we compared M06-L predicted relative nuclear magnetic shielding constants[4] to the measured chemical shifts. We calculated the isotropic nuclear magnetic shielding for phosphorous for $[Ph_3PAu]^+$ coordinated with $MeNO_2$, penta-2,3-diene, and methyl carbazate. Using the chemical shift for the solvent coordinated species of δ=30.3 ppm, we calculated a relative nuclear magnetic shielding for the allene coordinated structure of Δδ=+13.4 ppm which compares well to the relative chemical shift Δδ= +15.5 ppm observed.[5]

*Hammett Analysis of Formation of **2** from **1** and Methyl carbazate.*

The rate of reaction for each catalyst was determined by monitoring the rate of disappearance of allene at 6 mol % catalyst loadings. The general procedure for kinetics was used with methyl carbazate (20.3 mg, 225 mmol), 0.4 mL of a standard solution containing **1** (22.4 mg, 90.0 mmol, per aliquot) and 1,3,5-tri-tert-butylbenzene (7.40 mg, 30.0 mmol, per aliquot) (internal standard) in CD_3NO_2, and 0.2 mL of a standard solution containing PAr_3AuNTf_2 (3.99-5.09 mg, 5.40 mmol, per aliquot) in CD_3NO_2. The reactions were heated to 45 ºC and monitored by ^1H NMR until 80-85% conversion was reached. The rate data reported reflects an average of three independent kinetics experiments for reaction with each PAr_3AuNTf_2 catalyst. Hammett Analysis provide $\rho = 0.224$ and $R^2 = 0.9572$ (Figure S14, Table S3), suggesting that positive charge is diminishing in the rate determining transition state.

Figure S14. Hammett plot for the reaction, with 6 mol% catalyst loading.



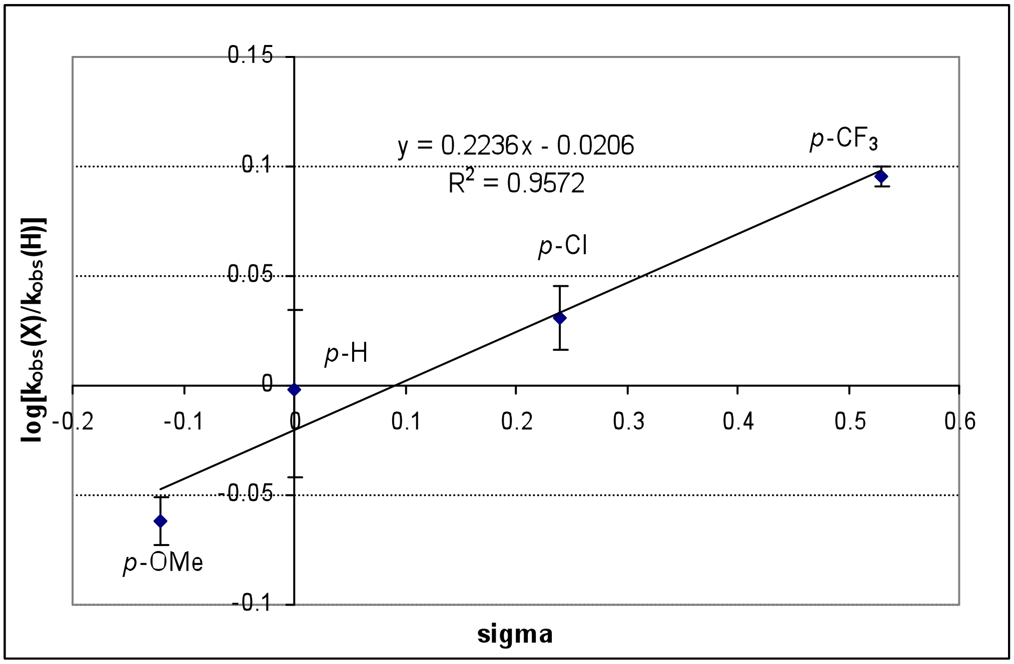
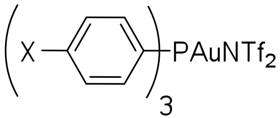


Table S3. Measured k_{obs} for various catalysts at 6 mol% catalyst loading.

	Trial 1 (h^{-1})	Trial 2 (h^{-1})	Trial 3 (h^{-1})	Average (h^{-1})
CF_3	0.422(3)	0.415(5)	0.424(6)	0.161(14)
Cl	0.376(3)	0.355(6)	0.356(8)	0.336(29)
H	0.368(11)	0.311(6)	0.328(3)	0.535(15)
MeO	0.289(2)	0.288(6)	0.301(6)	0.728(11)

Reversibility of reaction.

Resubjecting Chiral Products to Racemic Reaction Conditions.

Enantioenriched **2** (9.0 mg, 26.6 μmol, 56% ee) was added to a solution of methyl carbazate (4.79 mg, 53.2 μmol) and $Ph_3PAuNTf_2$ (1.97 mg, 2.66 μmol) in CH_3NO_2 in a scintillation vial equipped with magnetic stir bar and protected from ambient light. The resulting solution was stirred and heated to 45 °C for 6 h. The crude reaction mixture was passed through a silica plug, eluting with 1:1 EtOAc:hexanes. The organics were concentrated and flashed on SiO_2, eluting with 1:4 EtOAc:hexanes, to obtain re-obtain **2** (9.0 mg, 99% yield, 56% ee). Enantioselectivity of the starting material and product was determined by HPLC on Chiralpak OD-H (90:10 hexanes:isopropanol, 0.5 mL/min) t_R 41.4 min (major), 47.2 min (minor).

Competition Experiments.

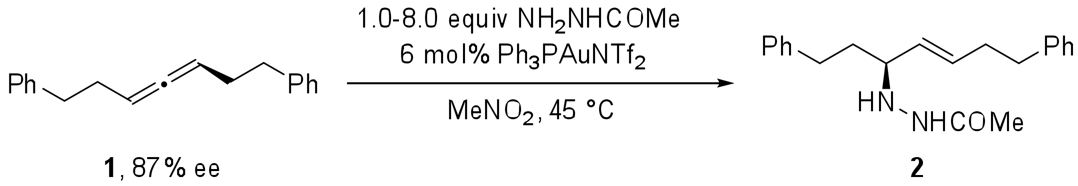
To a solution of **1** (11.2 mg, 45.0 μmol), $NH_2NHCOMe$ (4.1 mg, 45 μmol), and NH_2NHCO*t*Bu (17.8 mg, 135 μmol) in 300 μL $MeNO_2$, $Ph_3PAuNTf_2$ (3.99 mg, 5.4 μmol) was added. The solution was protected from light and stirred at 45 °C for 8 h. The crude reaction mixture was passed through a silica plug, eluting with 1:4 EtOAc:hexanes, to afford both **2** and **5** in a 15:85 ratio as determined by ^1H NMR with internal standard.

To a solution of **1** (10.0 mg, 29.5 μmol) and NH_2NHCO_2tBu (11.7 mg, 88.6 μmol) in 300 μL $MeNO_2$, $Ph_3PAuNTf_2$ (2.20 mg, 2.95 μmol) was added. The solution was protected from light and stirred at 45 °C for 8 h. The crude reaction mixture was passed through a silica plug, eluting with 1:4 EtOAc:hexanes, to afford **2** as the only product (10.0 mg, 99% yield).

Chirality Transfer.

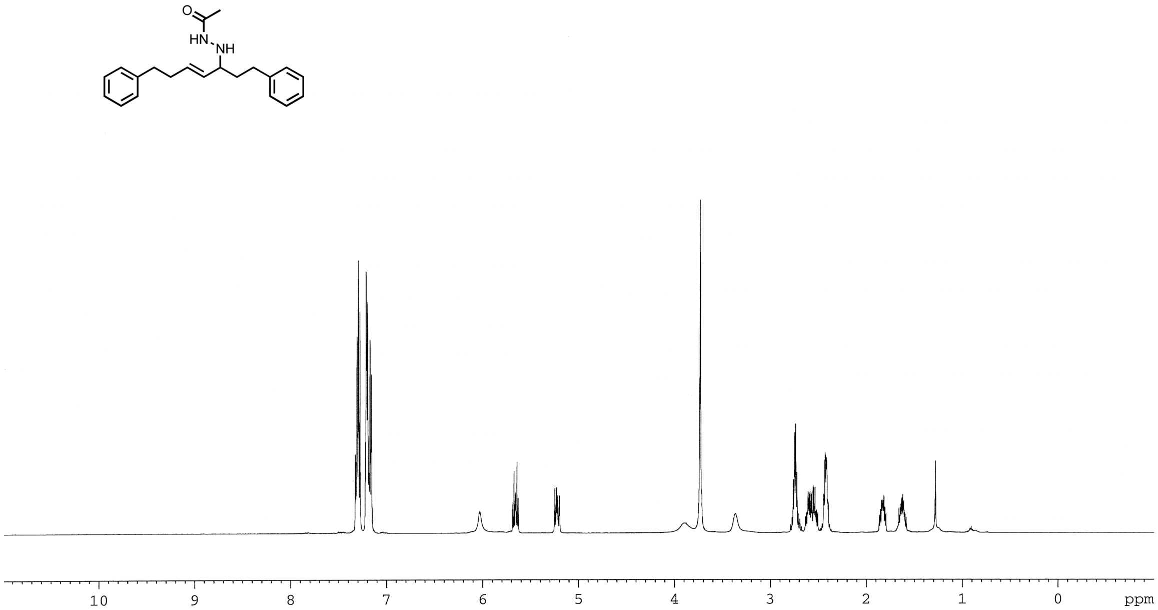
Enantioenriched **1** (85% ee) was prepared from the corresponding chiral propargyl alcohol by the method described by Myers.[6] To a solution of **1** (10.9 mg, 40.3 μmol), methyl carbazate (3.6-29.0 mg, 40.3-322 μmol) in 400 μL $MeNO_2$, $Ph_3PAuNTf_2$ (3.99 mg, 5.4 μmol) was added. The solution was protected from light and stirred at 45 °C for 12 h. The crude reaction mixture was flashed directly on 1:4 EtOAc:hexanes to provide the desired product (10.1 to 11.1 mg, 75-81% yield) (Table S4).

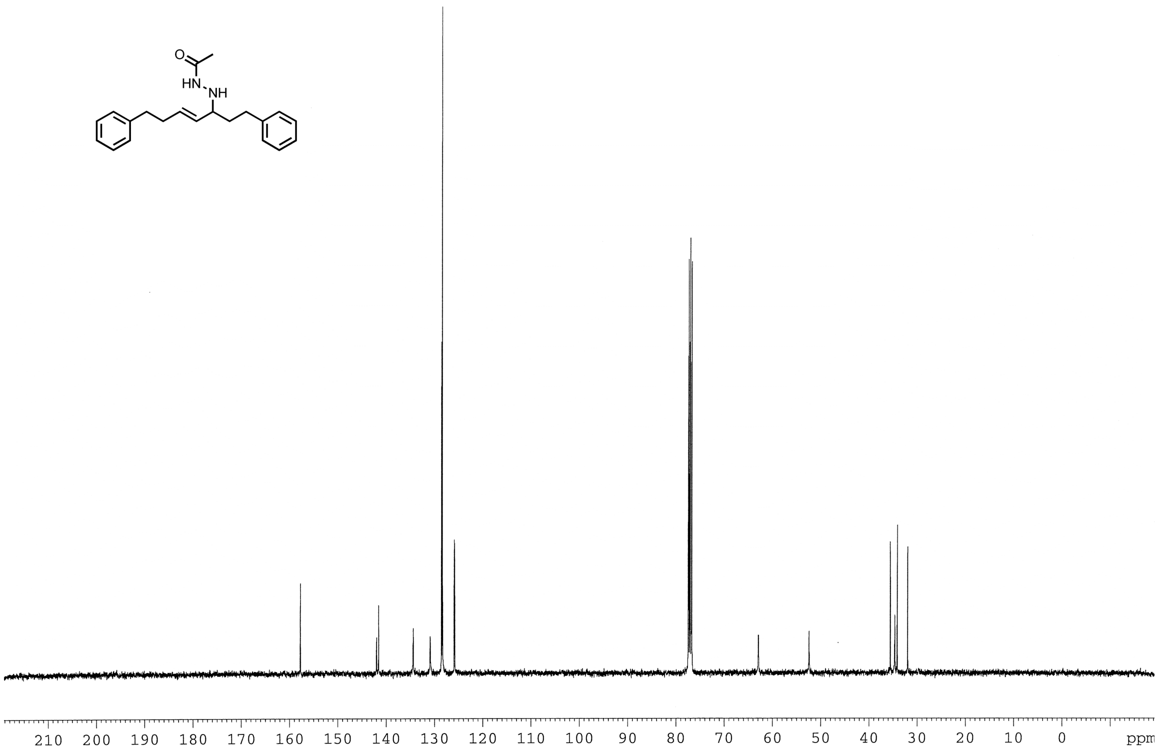
Table S4. Chirality transfer at 1.0 to 8.0 equiv of methyl carbazate.



Equiv of Nuc	yield (%)	ee (%)
1.0	81	28
2.0	75	48
4.0	81	56
8.0	79	56

III. Additional Spectral Data





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[1] Mezailles, N.; Ricard, L.; Gagosz, F.; *Org. Lett.* **2005**, *7*, 4133.

[2] Yamaguchi, M.; Hayashi, A.; Minami, T.; *JOC* **1991**, *56*, 4091.

[3] Takaya, J.; Iwasawa, N.; *J. Am. Chem. Soc.* **2008**, *130*, 15254.

(4) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2008**, *112*, 6794.

(5) We also considered the coordination of methyl carbazate by the N or O atoms. Our calculations suggest that the predicted relative nuclear shielding for the methyl carbazate structure is more consistent with an oxygen coordination (calculated $\Delta\delta = 1.2$ ppm, vs. $\Delta\delta = 0.6$ ppm from experiment) than the nitrogen coordination (calculated $\Delta\delta = -4.2$ ppm).

[6] Myers, A.G.; Zheng, B.; *J. Am. Chem. Soc*. **1996**, *118*, 4492.