Gold(I)-Catalyzed Intermolecular Hydroamination of Allenes with Arylamines

Alethea N. Duncan, Ross A. Widenhoefer*

French Family Science Center, Duke University, Durham, NC 27708, USA
Fax +1(919)660-1605; E-mail: rwidenho@chem.duke.edu

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Abstract: A mixture of [P(t-Bu)$_2$-o-biphenyl]AuCl and AgOTf catalyzes the intermolecular hydroamination of monosubstituted and 1,1- and 1,3-disubstituted allenes with primary and secondary arylamines.

Key words: allylations, allenes, amines, homogenous catalysis, regioselectivity

The transition-metal-catalyzed addition of the N–H bond of an amine across the C=C bond of an allene represents an attractive, atom economical approach to the synthesis of allylic amines.[1] Although a number of general and efficient methods have been developed for the intramolecular hydroamination of allenes,[2,3] effective methods for the intermolecular hydroamination of allenes, particularly those that utilize alkyl- or arylamines, remain scarce.[4–12] Zirconium[4] and titanium[5] complexes catalyze the intermolecular hydroamination of allenes with amines to form imines via addition of nitrogen to the central carbon atom of the allene. Palladium(II) complexes catalyze the intermolecular hydroamination of allenes with arylamines to form allylic amines, but these methods are of limited scope.[6,7] More recently, Yamamoto has described gold(III)-[8] and gold(I)-catalyzed[9] methods for the intermolecular hydroamination of allenes with arylamines and morpholine, respectively although efficient hydroamination was restricted to monosubstituted and 1,3-disubstituted allenes. Bertrand has reported the hydroamination of allenes with ammonia catalyzed by a cationic gold(I) cyclic (alkyl)(amino)carbene (CAAC) complex under forcing conditions (≥ 155 °C).[10]

We have recently reported the regio- and diastereoselective intermolecular hydroamination of allenes with carbamates catalyzed by a gold(I) N-heterocyclic carbene (NHC) complex that displayed excellent scope with respect to the allene.[11] We therefore considered that gold(I) NHC complexes might also catalyze the intermolecular hydroamination of allenes with arylamines with improved substrate scope relative to extant protocols. During the course of these studies, Bertrand and co-workers reported the intermolecular hydroamination of allenes with arylamines catalyzed by a gold(I) CAAC complex.[12] Although this procedure extended the scope of allene hydroamination to include 1,1-disubstituted allenes, neither the requisite gold CAAC catalyst, nor the ligand from which it is derived are commercially avialable.[13] Here we report an operationally simple method for the intermolecular hydroamination of monosubstituted and 1,1- and 1,3-disubstituted allenes with primary and N-alkyl anilines catalyzed by a commercially available gold(I) complex under mild conditions.

The catalyst system optimized for the intermolecular hydroamination of allenes with carbamates proved only modestly effective for the intermolecular hydroamination of allenes with arylamines. As an example, treatment of aniline with 3-methyl-1,2-butadiene (**1**; 2 equiv) and a catalytic 1:1 mixture of (IPr)AuCl [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine] and AgOTf in toluene at room temperature for 24 hours led to 10% conversion to form N-prenylaniline (**2a**) as the exclusive product (Table 1, entry 1). Substitution of the sterically hindered o-biphenyl phosphine ligand P(t-Bu)$_2$-o-biphenyl (**3**) for IPr and dioxane for toluene increased the conversion under these conditions to 35% (Table 1, entry 3). Raising the temperature to 45 °C led to complete consumption of aniline after 12 hours to form a 4.1:1 mixture of **2a** and N,N-diprenylaniline (**2b**; Table 1, entry 4). Aniline derivatives **2a** and **2b** were isolated in 73% and 17% yield, respectively, from the corresponding preparative-scale reaction of **1** with aniline (Table 2, entry 1). Control experiments ruled out silver- and acid-catalyzed pathways for the hydroamination of **1** with aniline (Table 1, entries 5–7).

In addition to aniline, a number of primary arylamines reacted with **1** (2 equiv) to form the corresponding N-prenylaniline derivatives in good to excellent yield with exclusive formation of the regioisomer resulting from attack of aniline at the less substituted allene terminus (Table 2, entries 2–11).[14] p-Nitro- and p-bromoaniline were highly active nucleophiles that reacted with **1** (2 equiv) at 45 °C for 12 hours to form mixtures of the corresponding N-prenyl- and N,N-diprenylaniline derivatives (Table 2, entries 6 and 7). However, increasing the **1**/aniline ratio to 3:1 led to exclusive formation of the N,N-diprenylanilines in excellent yield as single regioisomers (Table 2, entries 8 and 9). *Ortho*-substituted anilines proved highly selective nucleophiles for the gold(I)-catalyzed hydroamination of **1**, leading to formation of the N-prenylanilines in good to excellent yield without formation of the corresponding N,N-diprenylanilines (Table 2, entries 2–4, 10 and 11).

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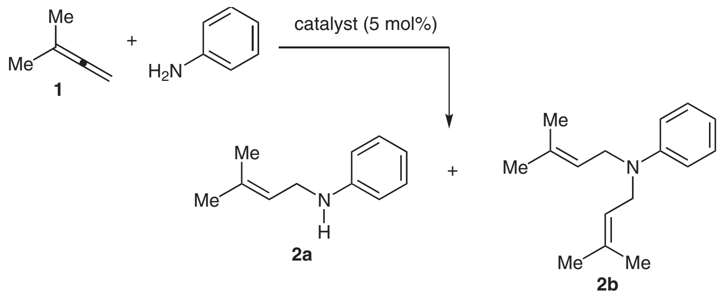
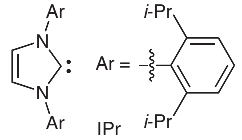
Table 1 Gold(I)-Catalyzed Hydroamination of 3-Methyl-1,2-butadiene (**1**; 0.8 M) with Aniline (0.4 M) as a Function of Ligand and Reaction Conditions

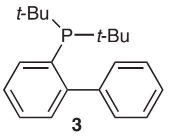


1 **2a** **2b**

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Conv (%)[a]	**2a/2b**[a]
1	(IPr)AuCl–AgOTf	toluene	25	24	10	>25:1
2	(IPr)AuCl–AgOTf	dioxane	25	24	17	>25:1
3	(**3**)AuCl–AgOTf	dioxane	25	24	35	>25:1
4	(**3**)AuCl–AgOTf	dioxane	45	12	100	4.1:1
5	AgOTf	dioxane	45	12	0	–
6	**3**–AgOTf	dioxane	45	12	0	–
7	**3**–HOTf	dioxane	45	12	0	–



IPr



3

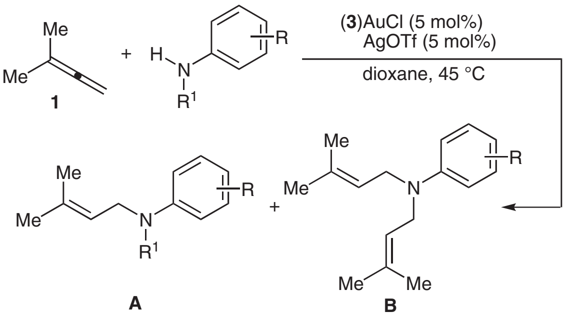
[a] Conversion and product ratio determined by GC analysis versus hexadecane internal standard.

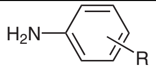
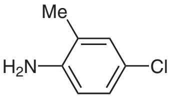
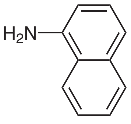
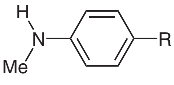
N-Methylanilines were also effective nucleophiles for the gold(I)-catalyzed hydroamination of **1**, forming the corresponding *N*-methyl-*N*-prenylanilines in good yield as single regioisomers (Table 2, entries 12 and 13). Dialkylamines, however, were not effective nucleophiles for the hydroamination of allenes under these conditions.

In addition to 3-methyl-1,2-butadiene (**1**), monosubstituted, functionalized 1,1-disubstituted, and 1,3-disubstituted allenes also underwent gold(I)-catalyzed intermolecular hydroamination with arylamines in good yield with good regio- and diastereoselectivity (Table 3). As an example of the hydroamination of a monosubstituted allene, reaction of *m*-bromoaniline with 1-cyclohexyl-1,2-propadiene at 45 °C for 24 hours led to isolation of *N*-(3-cyclohexyl-2-propenyl)aniline (**4**) in 91% yield as a 5.2:1 mixture of *E*- and *Z*-isomers (Table 3, entry 1). As an example of the hydroamination of a 1,3-disubstituted allene, reaction of *m*-bromoaniline with 1-phenyl-1,2-butadiene at 45 °C for 24 hours led to isolation of the *N*-(1-methyl-3-phenyl-2-propenyl)aniline (**5**) in 86% yield as a >25:1 mixture of *E*- and *Z*-isomers resulting from addition of the nucleophile to the methyl-substituted allene terminus (Table 3, entry 4). As an example of the hydroamination of a functionalized 1,1-disubstituted allene, reaction of *m*-bromoaniline with ethyl 3-hexyl-3,4-pentadienoate formed *N*-allylic aniline **6** in 93% isolated yield as a 4.4:1 mixture of *Z*- and *E*-isomers (Table 3, entry 5).

Stereochemical analysis of the gold(I)-catalyzed intramolecular hydroamination of *N*-γ-allenyl carbamates[3] and the intermolecular hydroalkoxylation of allenes with alcohols[15] supported mechanisms involving outer-sphere attack of the nucleophile on a gold π-allene complex. Largely on the basis of these precedents, we proposed an outer-sphere mechanism for the gold(I)-catalyzed intermolecular hydroamination of allenes with carbamates.[11] Conversely, Yamamoto[8] and Bertrand[12,13] have proposed inner-sphere pathways for the gold-catalyzed intermolecular hydroamination of allenes with arylamines and ammonia. Therefore, we have considered both outer-sphere and inner-sphere mechanisms for the gold(I)-catalyzed intermolecular hydroamination of allenes with arylamines. In the former pathway, endoergonic displacement of aniline from **I** via the 16-electron, three-coordinate intermediate **II** would form gold(I) π-allene complex **III**. Outer-sphere attack of the aniline on **III** would then form the gold σ-alkenyl ammonium complex **IV**. Deprotonation of **IV** with free aniline followed by protonolysis of the Au–C bond of **V** would then release the *N*-prenylaniline with regeneration of **I**. Alternatively, β-migratory insertion of the coordinated allene into the Au–N bond of **II** would likewise generate **IV** (Scheme 1).

Table 2 Intermolecular Hydroamination of **1** (0.8 M) with Arylamines (0.4 M) Catalyzed by a Mixture of (**3**)AuCl (5 mol%) and AgOTf (5 mol%) in Dioxane at 45 °C



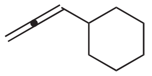
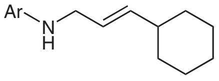
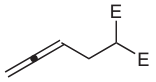
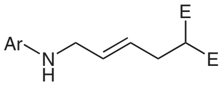
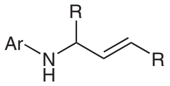
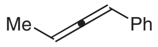
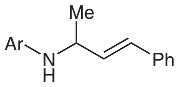
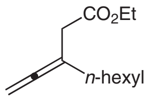
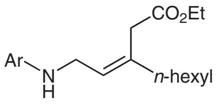
Entry	Aniline	Time (h)	Yield **A** (%)[a]	Yield **B** (%)[a]
1	 R = H	24	73	17
2	R = *o*-Br	24	87	0
3	R = *o*-*i*-Pr	24	83	0
4	R = *o*-*t*-Bu	24	66	0
5	R = *m*-Br	12	72	23
6	R = *p*-NO_2	12	33	66
7	R = *p*-Br	12	40	56
8	R = *p*-NO_2	12	0	99
9	R = *p*-Br	12	0	99
10		24	86	0
11		24	84	0
12	 R = H	24	73	–
13	R = Br	12	94	–

[a] Isolated yield of material of >95% purity.

[b] [Aniline]/[**1**] = 1:3.

In summary, we have developed an effective gold(I)-catalyzed protocol for the intermolecular hydroamination of allenes with arylamines to form *N*-allyl aniline derivatives with excellent regioselectivity and good diastereoselectivity. We continue to work toward the elucidation of the mechanism of gold(I)-catalyzed allene hydroamination and toward the development of effective methods for the catalytic hydroamination of allenes with alkyl amines.

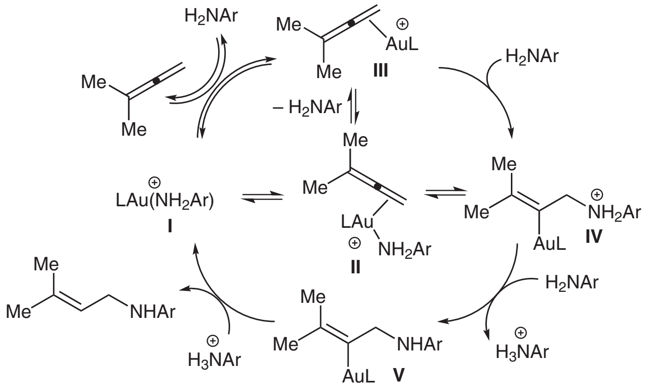
Table 3 Intermolecular Hydroamination of Monosubstituted, 1,3-Disubstituted, and Functionalized 1,1-Disubstituted Allenes with *m*-Bromoaniline Catalyzed by a Mixture of (**3**)AuCl (5 mol%) and AgOTf (5 mol%) in Dioxane at 45 °C

Entry	Allene	Product[a]	Yield (%)[b]	*E*/*Z*[c]
1		 **4**	91	5.2:1
2	 E = CO_2Me		72	>25:1
3	 R = *n*-pentyl		87	7.7:1
4		 **5**	86	>25:1
5		 **6**	93	1:4.4

[a] Ar = 3-BrC_6H_4.

[b] Isolated yield of material of >95% purity (*E* + *Z* isomers).

[c] *E*/*Z* ratio determined by ^{1}H NMR analysis of the purified reaction mixture.



Scheme 1 Potential mechanisms for the gold(I)-catalyzed hydroamination of **1** with aniline

Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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References and Notes

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(14) **Experimental Procedure and Spectroscopic Data for the Gold(I)-Catalyzed Hydroamination of 1 with *o*-Bromoaniline (Table 2, entry 2)**: Dioxane (0.50 mL) was added to a mixture of *o*-bromoaniline (39 mg, 0.23 mmol), (**3**)AuCl (6.2 mg, 1.1×10^{-2} mmol), and AgOTf (2.8 mg, 1.1×10^{-2} mmol) and the resulting suspension was stirred for 10 min at r.t. 3-Methyl-1,2-butadiene (**1**; 29 mg, 0.43 mmol) was added via syringe and the resulting mixture was stirred at 45 °C for 24 h. Column chromatography of the reaction mixture (SiO_2; hexanes–EtOAc, 15:1) gave *N*-(3-methyl-2-butenyl)-*o*-bromoaniline (48 mg, 87%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$ (dd, $J = 1.5, 8.5$ Hz, 1 H), 7.17 (dd, $J = 1.5, 7.8$ Hz, 1 H), 6.62 (dd, $J = 1.0, 8.3$ Hz, 1 H), 6.55 (dt, $J = 1.5, 7.5$ Hz, 1 H), 5.31–5.35 (m, 1 H), 4.23 (br s, 1 H), 3.72 (d, $J = 6.8$ Hz, 2 H), 1.76 (d, $J = 1.0$ Hz, 3 H), 1.72 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 145.1$, 136.1, 132.3, 128.4, 121.1, 117.5, 111.4, 109.7, 41.9, 25.7, 18.1. HRMS: *m/z* [M^+] calcd for $C_{11}H_{14}BrN$: 239.0310; found: 239.0313.

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