

Au(I)-Catalyzed Highly Efficient Intermolecular Hydroamination of Alkynes

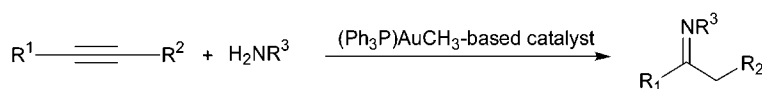
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Received July 16, 2003

ABSTRACT



Addition of aniline derivatives to aromatic and aliphatic alkynes proceeds efficiently in the presence of a gold(I) catalyst (0.01–1.0 mol %) to afford ketimines in good yields

Although the condensation between carbonyl compounds and primary amines is a well-established standard method for synthesizing imines,¹ hydroamination of alkynes^{2–4} attracts intense interest as an environmentally benign alternative route. By the development of new catalyst systems, the *intramolecular* hydroamination of alkynylamines has made significant progress.^{3,4} As for the *intermolecular* version on the other hand, the procedure involving aminomercuration of alkynes followed by demercuration is well-known.^{2c,d,5} However, the necessity of a stoichiometric amount of toxic mercury(II) reagents does not meet the contemporary re-

quirement against hazardous reagents. A wide range of metal catalysts of zinc, cadmium,⁶ mercury, thallium,⁷ zirconium,⁸ titanium,⁹ lanthanide,¹⁰ actinide,¹¹ ruthenium,¹² rhodium,¹³ and palladium¹⁴ have been examined for the catalytic

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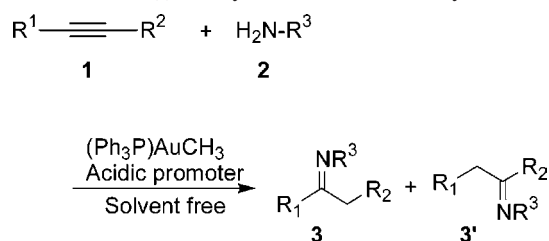
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hydroamination. In terms of the yield, catalytic efficiency, and simplicity of the procedure, however, the intermolecular hydroamination in the presence of these catalyst systems is not yet satisfactory for practical exploitation. Thus, the development of new catalyst systems remains an intriguing challenge.

Homogeneous catalysis by gold complexes has not been extensively explored.¹⁵ However, in 1987, Utimoto and co-workers reported the intramolecular hydroamination catalyzed by NaAuCl₄.¹⁶ Highly efficient gold(I)-catalyzed hydration of alkynes was also found by us recently.¹⁷ Continued research on gold-catalyzed reactions has uncovered that (Ph₃P)AuCH₃ in conjunction with acidic promoters, heteropoly acids in particular catalyze the intermolecular hydroamination far more efficiently than the foregoing metal-containing catalysts (Scheme 1). Preliminary observations are disclosed in this communication.

Scheme 1. Gold(I)-Catalyzed Intermolecular Hydroamination



As the reaction of phenylacetylene with *p*-bromoaniline indicates (Table 1), use of both (Ph₃P)AuCH₃ and an acidic promoter is an indispensable prerequisite for the hydroamination to take place. Thus, an attempted reaction using NH₄PF₆ or H₃PW₁₂O₄₀ alone without the gold precatalyst complex did not proceed at all. Another attempted reaction using the gold precatalyst in the absence of an acidic promoter did not work either (entry 1). However, the addition of acidic promoters activates the precatalyst to afford 4-bromo-*N*-(α -methylbenzylidene)aniline, though the efficiency depends on the nature of the promoter. Heteropoly acids are particularly effective (entries 2–4), resulting in near quantitative yields, the turnover numbers (TONs) being approximately 500/Au. Trifluoromethanesulfonic acid and dodecylbenzenesulfonic acid also serve as powerful promoters (entries 5 and 6), while methanesulfonic acid is inferior (entry 7). Ammonium hexafluorophosphate and tetrafluoroborate are able to activate, but only modestly or marginally (entries 8 and 9). Other ammonium salts and acids such as

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Table 1. Hydroamination of Phenylacetylene with 4-Bromoaniline^a

entry	promoter	yield of ketimine 3 (%) ^b
1	none	0
2	H ₃ PW ₁₂ O ₄₀	97
3	H ₃ MoW ₁₂ O ₄₀	95
4	H ₄ SiW ₁₂ O ₄₀	97
5	CF ₃ SO ₃ H	88
6	C ₁₂ H ₂₅ C ₆ H ₄ SO ₃ H	72
7	CH ₃ SO ₃ H	26
8	NH ₄ PF ₆	56
9	NH ₄ BF ₄	7
10 ^c	Nafion-SAC13	19

^a Reaction conditions: 0.002 mmol of (Ph₃P)AuCH₃, 0.01 mmol of promoter, 1 mmol of PhC≡CH, 1.1 mmol of 4-BrC₆H₄NH₂, 70 °C, 2 h.

^b Determined by 500 MHz ¹H NMR spectroscopy. ^c Performed with 0.013 g of Nafion-SAC13.

NH₄Cl, NEt₄Cl, NEt₄PF₆, H₂WO₄, and CH₃COOH were totally ineffective. Finally, it is interesting from the practical viewpoint to note that Nafion-SAC13, a polymer-supported sulfonic acid, does promote the gold-catalyzed reaction (entry 10), though the efficacy remains to be further enhanced.

The present hydroamination procedure has proved to be applicable to substituted anilines with various alkynes, both aromatic and aliphatic, inclusive of internal ones, as shown in Table 2. All the reactions were run under solvent-free conditions, using H₃PW₁₂O₄₀ as the acidic promoter in most cases.¹⁸

The reaction of aniline and phenylacetylene, using 0.2 mol % (Ph₃P)AuCH₃ and 1 mol % H₃PW₁₂O₄₀, proceeded to give *N*-(α -methylbenzylidene)aniline in 98% yield (Table 2, entry 1). However, when the precatalyst and promoter loadings were decreased to 0.01 and 0.05 mol %, respectively (20 mmol scale reaction), the yield of the ketimine dropped to 28%, although the TON reached 2800/Au (entry 2). 4-Bromoaniline reacted more smoothly even at lower loadings of the precatalyst and the promoter, resulting in high yields and TONs (entry 3, 94%, TON 940/Au; entry 4, 86%, TON 8600/Au). Other anilines having electron-withdrawing substituents such as 4-cyanoaniline and 4-nitroaniline reacted as well (entries 5–7, near 90% yields, TON 9000/Au in entry 6). In these reactions, the products were obtained as a mixture of the corresponding imine and enamine,¹⁹ the former being the major component. Steric hindrance in the aniline derivatives does not hamper the addition seriously, as the high-

(18) **Typical Experimental Procedure. Synthesis of 4-Bromo-*N*-(α -methylbenzylidene)aniline.** Under a nitrogen atmosphere, a mixture of phenylacetylene (2.17 g, 21 mmol), 4-bromoaniline (3.61 g, 21 mmol), (Ph₃P)AuCH₃ (1.0 mg, 0.0021 mmol), and H₃PW₁₂O₄₀ (30 mg, 0.01 mmol) was stirred at 70 °C for 14 h. After the mixture was cooled, hexane (25 mL) was added to the reaction mixture to precipitate out a white powder. The powder was recrystallized from hexane–dichloromethane to give 4-bromo-*N*-(α -methylbenzylidene)aniline (4.9 g, 18 mmol, 85% isolated yield).

(19) Presence of a tautomeric enamine component in the product was substantiated by the olefinic proton signals at 4.8 and 5.1 ppm for the product from *p*-cyanoaniline and 4.9 and 5.2 ppm for that from *p*-nitroaniline. In the reactions of other aniline derivatives, signals arising from enamines were not evident.

Table 2. Gold(I)-Catalyzed Hydroamination of Alkynes^a

entry	alkyne 1		amine 2		Au-cat. (mol %)	H ₃ PW ₁₂ O ₄₀ (mol %)	time (h)	yield of 3 (%) ^b
	R ¹	R ²	R ³					
1	C ₆ H ₅	H	C ₆ H ₅		0.2	1.0	2	98
2 ^c	C ₆ H ₅	H	C ₆ H ₅		0.01	0.05	24	28
3	C ₆ H ₅	H	4-BrC ₆ H ₄		0.1	0.5	2	94
4 ^c	C ₆ H ₅	H	4-BrC ₆ H ₄		0.01	0.05	14	86
5	C ₆ H ₅	H	4-NCC ₆ H ₄		0.1	0.5	1	88 (+6 ^d)
6 ^c	C ₆ H ₅	H	4-NCC ₆ H ₄		0.01	0.05	20	84 (+6 ^d)
7	C ₆ H ₅	H	4-NO ₂ C ₆ H ₄		0.1	0.5	1	86 (+7 ^d)
8	C ₆ H ₅	H	2,4,6-(CH ₃) ₃ C ₆ H ₂		0.2	1.0	2	93
9	4-FC ₆ H ₄	H	4-BrC ₆ H ₄		0.1	0.5	2	92
10	4-BrC ₆ H ₄	H	4-BrC ₆ H ₄		0.1	0.5	1	91
11	4-CH ₃ OC ₆ H ₄	H	4-BrC ₆ H ₄		0.1	0.5	0.25	90
12	1,4-diethynylbenzene		C ₆ H ₅ ^e		0.5	1.0	2	98 ^f
13	2-C ₄ H ₃ S ^g	H	C ₆ H ₅		0.5	1.0	2	87
14	<i>n</i> -C ₆ H ₁₃	H	C ₆ H ₅		0.2	1.0	3	96
15	<i>n</i> -C ₆ H ₁₃	H	4-BrC ₆ H ₄		0.2	1.0	2	96
16	<i>n</i> -C ₆ H ₁₃	H	4-CH ₃ OC ₆ H ₄		0.2	1.0	2	70
17	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	C ₆ H ₅		0.2	1.0	5	59
18	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	4-BrC ₆ H ₄		0.2	1.0	5	72
19 ^h	<i>n</i> -C ₃ H ₇	CH ₃	4-BrC ₆ H ₄		0.2	1.0	10	32 ⁱ + 29 ^j
20	C ₆ H ₅	H	C ₆ H ₅ NH		0.2	1.0 ^k	4	99

^a Reaction conditions: 1.0 mmol of alkyne **1**, 1.1 equiv of amine **2** with respect to **1**, 70 °C. ^b Determined by 500 MHz ¹H NMR spectroscopy. ^c Performed with 21 mmol of the alkyne and the amines. ^d Value in parentheses is the yield of the corresponding enamine. ^e Performed with 2.2 equiv of the amine relative to **1**. ^f Yield of 1,4-[C₆H₅N=C(CH₃)₂C₆H₄]. ^g 2-Thienyl group. ^h T = 60 °C. ⁱ Yield of **3**. ^j Yield of **3'**. ^k NH₄PF₆ was used instead of H₃PW₁₂O₄₀.

yielding reaction with 2,4,6-trimethylaniline verifies (entry 8). Other arylacetylenes substituted by either electron-withdrawing or -donating groups all reacted efficiently (entries 9–11). In particular, 4-methoxyphenylacetylene reacted rapidly as compared with other arylacetylenes (vide infra). 1,4-Diethynylbenzene readily reacted at both of the triple bonds by using of a 2.2 equiv amount of aniline (entry 12). 2-Ethynylthiophene also underwent the hydroamination, although it was somewhat less reactive than phenylacetylene, as judged by the higher catalyst loading (entry 13).

Aliphatic terminal alkynes displayed reactivities similar to aromatic alkynes as far as the H₃PW₁₂O₄₀ promoter was concerned (entries 14–16). Internal ones, less reactive due presumably to steric reasons, required longer reaction times to obtain acceptable yields (entries 17–19).

It is interesting to note that phenylhydrazine also adds to phenylacetylene, affording a high yield of the corresponding phenylhydrazone, which is an intermediate in Fischer indole synthesis (entry 20). Fukumoto and co-workers have recently reported the reaction of terminal alkynes with hydrazines catalyzed by a rhodium complex. However, the reaction proceeds in an entirely different route, forming nitriles through formal displacement of the terminal hydrogen with an NH₂ group.²⁰ On the other hand, titanium complexes have been known to catalyze the addition of hydrazines to alkynes, although the process needs higher catalyst loading.^{9h}

Despite the tremendous effort made, aliphatic amines did not add to alkynes under conditions similar to the aniline reactions.

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The gold(I)-catalyzed intermolecular hydroamination of alkynes with aromatic amines appears to involve electrophilic attack of the amine to alkynes. Experiments to more clearly reveal the influence of the substituents in the starting materials were carried out using NH₄PF₆, which was a modestly effective and hence more suitable promoter for the objective than H₃PW₁₂O₄₀. As the results summarized in Table 3 indicate, the reaction proceeds more smoothly when

Table 3. Hydroamination of Phenylacetylene Derivatives with Aniline Derivatives^a

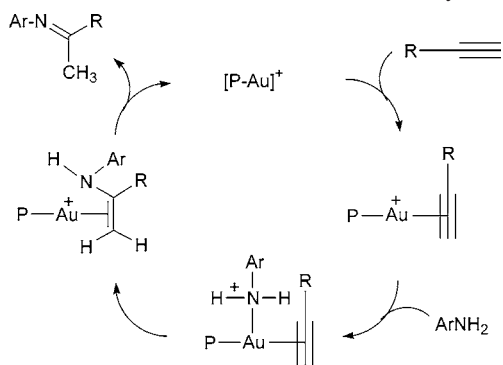
entry	alkynes 1		amines 2		yield of 3 (%) ^b
	R ¹	R ²	R ³		
1	C ₆ H ₅	H	4-NCC ₆ H ₄		92 ^c
2	C ₆ H ₅	H	4-BrC ₆ H ₄		91
3	C ₆ H ₅	H	C ₆ H ₅		46
4	C ₆ H ₅	H	4-CH ₃ OC ₆ H ₄		31
5	4-FC ₆ H ₄	H	4-BrC ₆ H ₄		24
6	4-BrC ₆ H ₄	H	4-BrC ₆ H ₄		20
7 ^d	4-CH ₃ OC ₆ H ₄	H	4-BrC ₆ H ₄		99

^a Reaction conditions: 1.0 mmol of alkyne **1**, 1.1 equiv of amine **2** relative to **1**, 0.2 mol % (PPh₃)AuCH₃, 1 mol % NH₄PF₆, 70 °C, 5 h. ^b Determined by 500 MHz ¹H NMR spectroscopy. ^c Obtained as a 92:8 mixture of the imine and enamine. ^d Reaction time = 3 h.

the amine substituent is more electron-withdrawing (entries 1–4) and the alkyne substituent is more electron-donating (entries 2, 5–7).

The reactivity trend can be rationalized by the mechanism illustrated in Scheme 2. Thus, analogously to Teles's

Scheme 2. Plausible Reaction Pathway



mechanistic proposal for the methanol addition to alkynes,^{16b,21} the cationic gold(I) species, $\text{Au}(\text{PPh}_3)^+$, generated by protonolysis of $(\text{Ph}_3\text{P})\text{AuCH}_3$, is envisaged to interact with an

(21) Role of ammonium salts derived from the acidic promoters and **2** in the present reaction system remains to be further clarified. A similar promoting effect of ammonium salts has been reported in the $[\text{Ru}_3(\text{CO})_{12}]$ -catalyzed hydroamination; see ref 12b.

alkyne, forming a cationic Au(I)–alkyne complex. Complex formation should be favored by an electron-donating substituent in the alkyne molecule, as was indeed observed. Two reaction pathways for an amine to react with the gold(I)–alkyne complex can be considered. One is direct intermolecular nucleophilic attack of the amine on the alkyne ligated to the gold center. However, this route is less likely since an aniline that has a more electron-withdrawing substituent reacts faster. The other route, involving coordination of the amine to the gold center prior to the C–N bond formation, appears more probable.²²

In conclusion, we have demonstrated that the combination of $(\text{Ph}_3\text{P})\text{AuCH}_3$ and acidic promoters efficiently catalyzes hydroamination of alkynes with anilines. The catalytic activity is much higher than that observed with the other catalyst systems so far reported. We believe that the new findings will be useful for developing a practical process.

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(22) In the gold(III)-catalyzed intramolecular hydroamination to afford cyclic imines, direct attack of amine to the coordinated alkyne was illustrated; see ref 16. On the other hand, in the gold(I)-catalyzed methanol addition to alkynes, an associative mechanism involving coordination of methanol to gold was predicted by ab initio calculations; see ref 16b.