

# A Highly Efficient Three-Component Coupling of Aldehyde, Alkyne, and Amines via C–H Activation Catalyzed by Gold in Water

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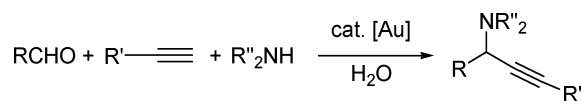
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The increasing environmental consciousness of the chemical community has led to the search for more efficient and environmentally friendly methods for chemical syntheses.<sup>1</sup> One of the related research areas has been the development of Barbier–Grignard type reactions in water.<sup>2</sup> Representative examples include allylation,<sup>3</sup> propargylation,<sup>4</sup> benzylation,<sup>5</sup> arylation/vinylation,<sup>6</sup> and the aldol-type reaction.<sup>7</sup> A Barbier–Grignard type carbonyl alkylation with nonactivated halides in water has also been developed.<sup>8</sup> On the other hand, an alternative reaction via catalytic C–H activation<sup>9</sup> in water by using a water-soluble catalyst would provide an atom-economical approach<sup>10</sup> for such reactions.

Recently, we<sup>11</sup> and others<sup>12</sup> have described Grignard-type reactions of alkyne to aldehyde and imines to generate propargyl alcohols and via catalytic C–H activation in water and organic media. A highly enantioselective addition of alkynes to imines to generate optically propargylamines in water by using a chiral copper catalyst has also been developed by us.<sup>13</sup> However, the previous methods in water are largely limited to imines generated from arylamines and aromatic aldehydes. As a continued interest to develop efficient synthesis of propargylamines via activation of alkynes, herein we report a highly efficient three-component-coupling of aldehyde, alkynes, and amines (A<sup>3</sup> Coupling) catalyzed by gold in water (Scheme 1). The reaction is general and can be applied to both aromatic and aliphatic aldehydes and amines. Nearly quantitative yields were obtained in most cases. Furthermore, no cocatalyst or activator (as in the ruthenium- and copper-catalyzed imine additions) is required, less than 1 mol % of catalyst is needed, and water is the only byproduct for the reaction.

## Scheme 1



Compared to other late transition metals, gold has not been extensively explored as a catalyst. However, recent work by Ito,<sup>14</sup> Hashmi,<sup>15</sup> and others<sup>16</sup> has demonstrated unique catalytic properties of gold in several reactions. Whereas only ca. 10% of the corresponding product was obtained by using CuBr, the three-component coupling of benzaldehyde, piperidine, and phenylacetylene in the presence of 5 mol % AuCl afforded quantitative yield of the desired propargylic amine as shown by the <sup>1</sup>H NMR of the crude reaction mixture (see Table 1). No other additive was needed for this reaction. Subsequently, gold salts such as AuCl, AuI, AuBr<sub>3</sub>, and AuCl<sub>3</sub> were tested, and all showed excellent catalytic activities. Au(III) salts seemed slightly better than Au(I) salts. Even when only 0.25 mol % AuBr<sub>3</sub> was used as the catalyst, the conversion of the reaction still was as high as 99% (the yield, 98%). Even with only 0.01 mol % AuBr<sub>3</sub> used as the catalyst, the reaction still led

**Table 1.** Three-component Coupling of Benzaldehyde, Piperidine, and Phenylacetylene Catalyzed by Gold in Water

entry	catalyst (mol %)	solvent/temp (°C)/time (h)	conversion (%) <sup>a</sup>
1	AuCl (5)	H <sub>2</sub> O/100/12	99
2	AuCl (1)	H <sub>2</sub> O/100/12	99
3	AuI (1)	H <sub>2</sub> O/100/12	99
4	AuBr <sub>3</sub> (1)	H <sub>2</sub> O/100/12	100
5	AuCl <sub>3</sub> (1)	H <sub>2</sub> O/100/12	100
6	Au <sup>0</sup> sponge (3)	H <sub>2</sub> O/100/12	0
7	AuBr <sub>3</sub> (0.25)	H <sub>2</sub> O/100/12	99
8	AuBr <sub>3</sub> (1)	H <sub>2</sub> O/100/2	93
9	AuBr <sub>3</sub> (1)	H <sub>2</sub> O/100/5.5	100
10	AuBr <sub>3</sub> (1)	H <sub>2</sub> O/r.t./72	81
11	AuBr <sub>3</sub> (1)	THF/r.t./48	55 <sup>b</sup>
12	AuBr <sub>3</sub> (1)	toluene/100/12	78 <sup>b</sup>
13	AuBr <sub>3</sub> (1)	DMF/100/12	62 <sup>b</sup>

<sup>a</sup> Conversions were determined by <sup>1</sup>H NMR of the crude reaction mixture.

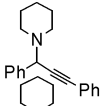
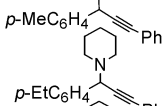
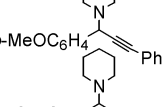
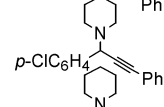
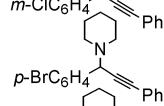
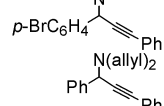
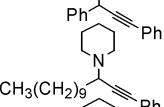
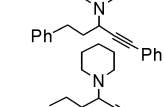
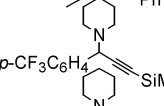
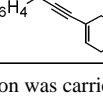
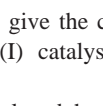
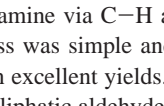
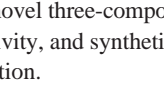



<sup>b</sup> Various byproducts were observed.

to 13% conversion during the same reaction period. As AuBr<sub>3</sub> is relatively cheaper among these gold salts and the most effective, it was therefore chosen as the catalyst for other substrates. Gold metal itself did not show any catalytic activity. No reaction was observed in the absence of Au(I) or Au(III) or when the reaction was carried out under an atmosphere of air. The nature of the reaction media significantly affects the reaction. Whereas reactions proceeded cleanly in water, the use of organic solvent such as THF, toluene, and DMF resulted in a low conversion and more byproducts.

The catalysis was then applied to various aldehydes and dialkylamines as summarized in Table 2. Both aromatic and aliphatic aldehydes, including those bearing functional groups such as alkoxy, chloro, bromo, and trifluoromethyl additions, were able to undergo the corresponding three-component-coupling. Aryl aldehydes with electron-donating groups (entries 2, 3, 4, and 5) reacted smoothly; however, as 4-methoxybenzaldehyde and 4-alkylbenzaldehyde showed, electron-rich groups bound to the benzene ring decreased the reactivity and required a longer reaction time. Electron-withdrawing groups (entries 6, 7, 8, 9, and 10) displayed high reactivities; reactions were completed at a lower temperature and gave higher conversions. The decreased yield for aliphatic aldehydes is caused by the trimerization of aliphatic aldehydes. The corresponding amine also has an effect on the reaction: whereas dialkylamines reacted smoothly in these conditions, aniline formed the corresponding product in lower yields, and *N*-alkylanilines and 1° amines were inert for the reactions. Aliphatic alkynes also worked effectively (entries 15 and 16).

A tentative mechanism was proposed (see Scheme 2) involving the activation of the C–H bond of alkyne by a Au(I) species<sup>17</sup> (for AuBr<sub>3</sub>-catalyzed, Au(I) can be generated in situ from reduction of Au(III) by the alkyne). The gold acetylide intermediate thus generated reacted with the immonium ion generated in situ

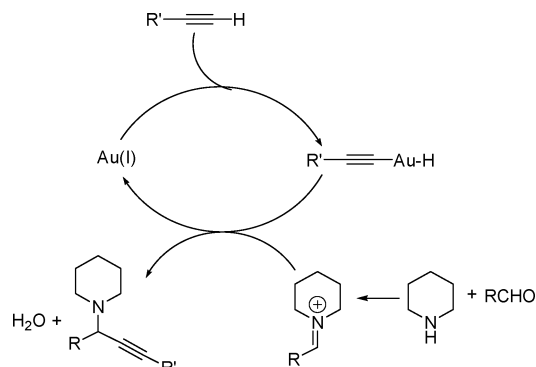
**Table 2.** Coupling of Aldehyde, Alkyne, and Amine Catalyzed by Gold in Water

entry	aldehyde	amine	product	yield <sup>a</sup>
1	PhCHO	piperidine		>99%
2	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CHO	piperidine		87%
3	<i>p</i> -EtC <sub>6</sub> H <sub>4</sub> CHO	piperidine		95%
4	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CHO	piperidine		91%
5	<i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO	piperidine		98% <sup>b</sup>
6	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CHO	piperidine		>99%
7	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub> CHO	piperidine		>99%
8	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CHO	piperidine		>99%
9	<i>m</i> -BrC <sub>6</sub> H <sub>4</sub> CHO	piperidine		>99%
10	PhCHO	HN(allyl) <sub>2</sub>		95%
11	PhCHO	HN(Bn) <sub>2</sub>		99%
12	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> CHO	piperidine		53%
13	PhCH <sub>2</sub> CHO	piperidine		75%
14	 CHO	piperidine		96%
15	<i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO	piperidine		>99%
16	<i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO	piperidine		>99%

<sup>a</sup> Isolated yields based on aldehyde. <sup>b</sup> Reaction was carried out at 70 °C.

from aldehydes and secondary amines to give the corresponding propargylamine and regenerate the Au(I) catalyst for further reactions (Scheme 1).

In conclusion, a highly efficient gold-catalyzed three-component-coupling of aldehyde, alkyne, and amine via C–H activation has been achieved in water. The process was simple and generated a diverse range of propargylamines in excellent yields. The reaction is applicable to both aromatic and aliphatic aldehydes and amines. Water is the only byproduct in this novel three-component reaction. The scope, mechanism, stereoselectivity, and synthetic applications of this reaction are under investigation.

**Scheme 2.** Tentative mechanism for the gold-catalyzed reaction in water

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**Supporting Information Available:** Representative experimental procedure and characterization of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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