

The First Silver-Catalyzed Three-Component Coupling of Aldehyde, Alkyne, and Amine

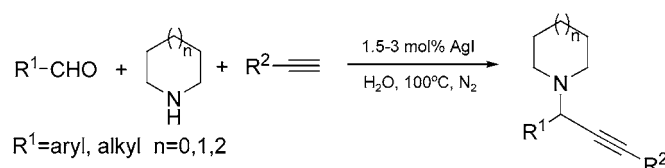
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ABSTRACT



Silver iodide catalyzed the three-component coupling of aldehyde, alkyne, and amines to generate propargylic amines with high efficiency in water. The silver-catalyzed reaction is especially effective for reactions involving aliphatic aldehyde. No additional cocatalyst or activator is required.

In comparison with other transition metals, silver has been virtually untouched as a catalyst for coupling purposes. Very recently, a few silver-catalyzed reactions such as aza-Diels–Alder reaction,¹ asymmetric aldol reaction,² addition,³ coupling,⁴ cyclization,⁵ and allylation⁶ have been reported; however, in most cases, the silver species served as either a cocatalyst or a Lewis acid. Silver “catalysts” in a “transition metal” sense are commonly considered to have low efficiency

and not to be as good as other late transition metals. On the other hand, the development of environmentally friendly synthetic methods has become an increasingly important consideration for many chemists.⁷ One such subject is the development of the Barbier–Grignard-type reaction in water. With the low atom economy of the classical Barbier–Grignard-type reaction generating stoichiometric amounts of metal ions and halides, an alternative reaction via catalytic C–H activation would provide a greener approach for such reactions. Recently, we⁸ and others^{9,10} have described the direct addition of terminal alkyne to aldehyde and imines to

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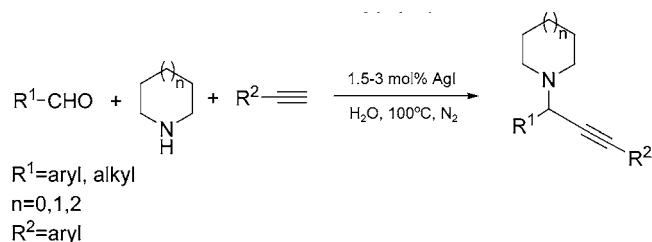
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Scheme 1



afford propargyl alcohol and propargylamines. With Cu(I)-pybox as a chiral catalyst, a highly enantioselective imine addition in either water or toluene was developed.¹¹ We also developed the coupling of alkynes with *N*-acylimines and *N*-acyliminium ions mediated by a CuBr catalyst.¹² Because of our continued interest in synthesizing propargylamine via activation of alkynes, we found that gold can be used as a highly efficient catalyst for a three-component coupling reaction of aldehyde, alkyne, and amine in water.¹³ However, previous success in such three-component couplings has been largely limited to the aromatic aldehydes. Aliphatic aldehydes have led to both low yields and conversions.

Herein we wish to report that AgI is a highly effective catalyst for the three-component coupling of aldehyde, alkyne, and amine to generate propargylamines in water, without using any other cocatalyst or additives (Scheme 1). Furthermore, a reversal of the reactivity of aliphatic and aromatic aldehydes was observed compared to our early reported systems, in which aliphatic aldehydes were often much more reactive than aromatic aldehydes.

In an effort to seek a more effective catalyst for the coupling of aldehyde, alkyne, and amines, water-soluble or partially soluble salts such as AgNO₃, Ag₂O, AgOAc, Ag₂SO₄, AgOTf, AgBF₄ were all found to catalyze the reaction of benzaldehyde, piperidine, and phenylacetylene with low conversion (ca. 25–45%) together with the formation of some carboxylic acid. Metal silver did not show any catalytic activity. To reduce the consumption of the catalyst due to reduction by aldehyde, we screened some water-insoluble

Table 1. Silver-Catalyzed Reaction of Benzaldehyde, Piperidine and Phenylacetylene in Water^a

| entry | catalyst (3 mol %) | time (h) | conversion (%) |
|-------|---------------------------------|----------|----------------|
| 1 | AgOTf | 14 | 40 |
| 2 | AgBF ₄ | 14 | 35 |
| 3 | Ag ₂ O | 14 | 40 |
| 4 | Ag ₂ SO ₄ | 14 | 42 |
| 5 | AgNO ₃ | 14 | 40 |
| 6 | AgF | 14 | 40 |
| 7 | AgCl | 14 | 55 |
| 8 | AgBr | 14 | 60 |
| 9 | AgI | 14 | 75 |

^a All reactions were carried out on 1 mmol scale based on aldehyde; conversions were based on ¹H NMR measurement of crude reaction mixtures.

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

| entry | aldehyde | amine | alkyne | product | yield ^a |
|-------|----------|-------|--------|---------|--------------------|
| 1 | | | | | 96% |
| 2 | | | | | 89% |
| 3 | | | | | 91% |
| 4 | | | | | 99% |
| 5 | | | | | 96% |
| 6 | | | | | 83% |
| 7 | | | | | 79% |
| 8 | | | | | 85% |
| 9 | | | | | 88% |
| 10 | | | | | 70% ^b |
| 11 | | | | | 95% ^b |
| 10 | | | | | 60% ^b |
| 11 | | | | | 47% ^b |
| 12 | | | | | 64% |

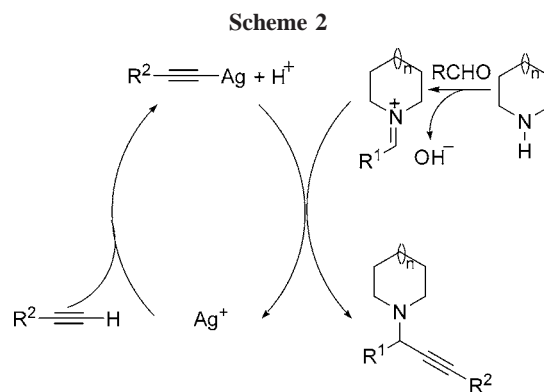
^a Isolated yields based on aldehyde were reported; carried out on a 2 mmol scale with aldehyde/amine/alkyne = 1:1.2:1.5 and 1.5 mol % AgI, 100 °C, 1 mL of water. ^b Carried out on a 1 mmol scale with 3% AgI under the same conditions.

Ag salts. No desired product was found with Ag₂S. However, AgCl, AgBr, and AgI showed good results, and AgI was found to be the most effective in catalyzing the three-component coupling. No other additive was needed for this reaction. The reaction did not proceed in the absence of AgI or under an air atmosphere.

Subsequently, various aldehydes, alkynes, and dialkylamines were similarly coupled and the results were sum-

marized in Table 2. Both aromatic and aliphatic aldehydes were able to undergo addition to afford the corresponding¹² three-component propargylic amines effectively. While only a trace amount of product was obtained with acyclic amines (such as diallylamine), cyclic dialkylamines and various terminal alkynes reacted well in these conditions. However, the reaction was found to be highly affected by the nature of the aldehyde. Aryl aldehyde decreased the reactivity of the reaction, required a longer reaction time for reaction completion, and gave lower conversions and lower yields. Aliphatic aldehydes, on the other hand, displayed higher reactivity and cleaner reactions. The reactions involving aliphatic aldehydes gave both higher conversions and greater yields. While unwanted trimerization of aldehyde was a major limitation of the reactions catalyzed by gold and copper, almost no trimer was formed with aliphatic aldehydes when using AgI as the catalyst. The reactions proceeded very well in either water or an organic solvent such as toluene and DMF. The conversions of coupling cyclohexylcarboxaldehyde, piperidine, and phenylacetylene in toluene and DMF were 95 and 98%, respectively. Even when only 0.2 mol % AgI was used as a catalyst, the reaction in water still led to more than 95% conversion and an isolated yield of 92%. A tentative mechanism was proposed involving the exchange of H of the C–H bond of alkyne by a Ag(I) species. The silver acetylide intermediate thus generated reacted with the iminium ion generated in situ from aldehydes

and secondary amines to give the corresponding propargylamine and regenerate the Ag(I) catalyst for further reactions (Scheme 2).



In conclusion, we have developed a highly effective three-component coupling of aldehyde, alkyne, and amine with silver as the catalyst. This process is simple and provides a diverse range of propargylamines in high yields. Aliphatic aldehydes are particularly effective for the reaction, which provides an effective complement of gold- and copper-catalyzed A^3 coupling. The scope, mechanism, and synthetic application of other silver-catalyzed couplings are under further investigation.¹⁴

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

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(14) A representative procedure: A mixture of AgI (7 mg, 0.03 mmol), cyclohexylcarboxaldehyde (244 μ L, 2.0 mmol), piperidine (210 μ L, 2.2 mmol), phenylacetylene (300 μ L, 3 mmol) in water (1 mL) was stirred at 100 °C oil-bath for 2 h under N_2 . The reaction mixture was cooled, extracted with ether (3×15 mL) and dried over $MgSO_4$. Analysis of the crude mixture by 1H NMR showed a quantitative conversion of aldehyde. The product was isolated by flash chromatography on silica gel (eluent: hexanes–EtOAc) to give propargylamine in almost quantitative yield (540 mg, 96%).