Copper(I)- and Gold(I)-catalyzed Synthesis of 2,4-Disubstituted Quinoline Derivatives from *N*-Aryl-2-propynylamines

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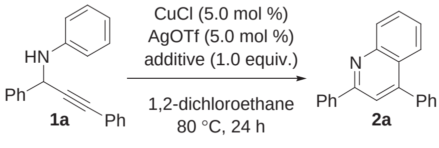
2,4-Disubstituted quinoline derivatives were obtained from *N*-aryl-2-propynylamines catalyzed by copper(I) and gold(I) complexes. The quinoline derivatives could also be obtained by the reaction of *N*-arylaldimines with terminal acetylenes via the formation of *N*-aryl-2-propynylamines.

Quinoline derivatives are important as functional materials[1] and medicines.[2] There have been several classical methods for the synthesis of quinolines; for example, Skraup,[3] Doebner–von Miller,[4] Friedländer, Combes,[5] and Ciamician–Dennstedt[6] procedures. Recently, electrophilic cyclization using iodine,[7] and metal-mediated[8] or -catalyzed[9] syntheses of quinoline derivatives have also been reported. We report herein the efficient synthesis of 2,4-disubstituted quinoline derivatives from *N*-aryl-2-propynylamines using the combination of copper(I)–silver or gold(I)–silver as a catalyst, and an aldimine as a hydrogen acceptor. The copper(I)–silver system is also effective for the direct formation of quinolines from aldimines and terminal acetylenes in one-pot.

Treatment of 2-propynylamine **1a** with catalytic amounts of copper(I) chloride and silver triflate in 1,2-dichloroethane at 80 °C for 24 h gave quinoline derivative **2a** in 38% yield (eq 1).[10–12] In this reaction, dihydrogen should be formed as a side product. By adding an aldimine **3**, which was derived from benzaldehyde and aniline, as a hydrogen acceptor,[13,14] the yield of **2a** increased dramatically and **2a** was obtained in 93% yield (eq 1).[15]

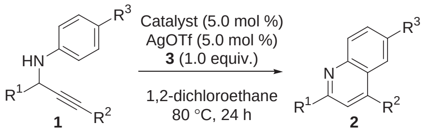


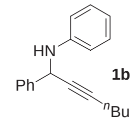
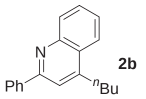
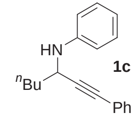
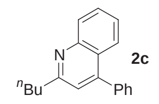
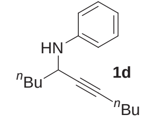
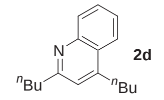
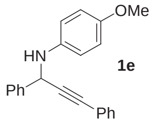
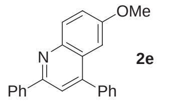
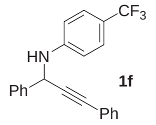
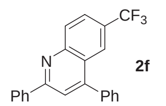
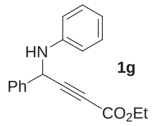
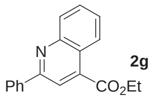
Additive	**2a**
—	38%
3	93%

(1)

By using a mixture of copper(I) chloride and silver triflate as a catalyst, 2-propynylamine bearing an alkyl group at either a terminal position of the acetylene moiety or the propargyl position, **1b** and **1c**, gave quinoline derivatives **2b** and **2c** in 78% and 73% yields, respectively (Table 1, Entries 1 and 3). The yields of quinoline derivatives increased when a combination of gold(I) chloride and silver triflate was used; **2b** and **2c** were obtained in 95% and 82% yields, respectively (Table 1, Entries 2 and 4). A 2-propynylamine possessing possessing alkyl groups at both a terminal position of the acetylene moiety and the propargyl position, **1d**, provided quinoline derivative **2d** in 19% and 51% yields, respectively (Table 1, Entries 5 and 6). With a 2-propynylamine having an electron-donating group at the para-position of the phenyl group on the nitrogen atom, **1e**, quinoline delivative **2e** was formed quantitatively (Table 1, Entries 7 and 8). On the other hand, a 2-propynylamine bearing an electron-withdrawing group, **1f**, provided quinoline derivative **2f** in 68% and 42% yields, respectively (Table 1, Entries 9 and 10).[16] The formation of quinoline derivative **2f** in moderate yield deserves special mention since it is usually difficult to carry out hydroarylation of acetylenes with aromatic compounds bearing electron-withdrawing group(s). A 2-propynylamine with an ester moiety at the terminal position of the acetylene moiety **1g** also produced the corresponding quinoline derivative **2g**, however the yield was low (Table 1, Entries 11 and 12).

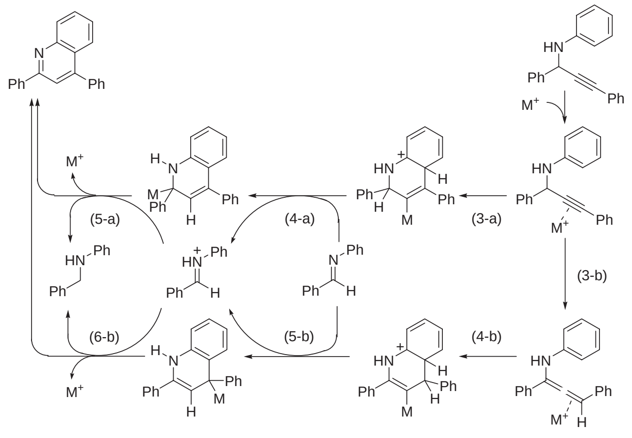
Table 1. Copper- and silver-catalyzed synthesis of quinolines from 2-propynylamines



Entry	**1**	Product (**2**)	Yield/%[a] Catalyst = CuCl	AuCl
1	 **1b**	 **2b**	78 (81)	
2				95 (>99)
3	 **1c**	 **2c**	73 (77)	
4				82 (86)
5	 **1d**	 **2d**	19 (23)	
6				51 (56)
7	 **1e**	 **2e**	96 (>99)	
8				96 (>99)
9[b]	 **1f**	 **2f**	68 (71)	
10[b]				42 (44)
11[c]	 **1g**	 **2g**	35 (38)	
12[d]				18 (20)

[a] Isolated yield. ^{1}H NMR yield is reported in parentheses. [b] 100 °C. [c] CuCl (10 mol %), AgOTf (10 mol %), 100 °C. [d] AuCl (10 mol %), AgOTf (10 mol %), 100 °C.

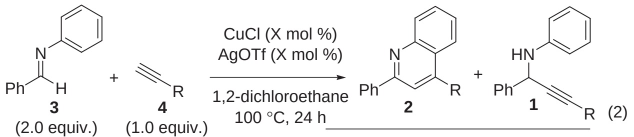
We consider the proposed mechanism as follows: (1) formation of copper(I) or gold(I) cation by the reaction of copper(I) chloride or gold(I) chloride with silver triflate; (2) coordination of a 2-propynylamine to the metal center. After this reaction



Scheme 1. Proposed mechanism for the formation of quinoline derivatives.

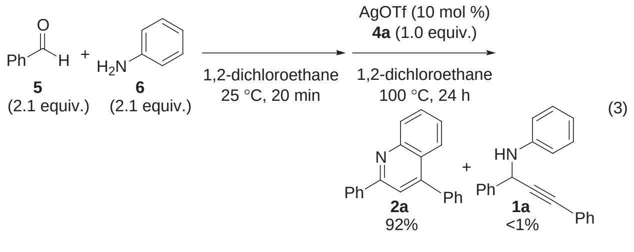
step, there are two possible pathways. Path A: (3-a) cyclization; (4-a) deprotonation and rearrangement of the metal center; (5-a) dehydride and elimination of the metal center. Path B: (3-b) isomerization of the 2-propynylamine to an arenylamine; (4-b) cyclization; (5-b) deprotonation and rearrangement of the metal center; (6-b) dehydridation and elimination of the metal center (Scheme 1).

Quinoline derivatives could also be synthesized by the reactions of aldimines with terminal acetylenes (eq 2). Treatment of an aromatic aldimine **3** with phenylacetylene (**4a**) in the presence of copper(I) chloride and silver triflate gave quinoline derivative **2a** in 91% yield (eq 2).[17,18] Alkylacetylene **4b** also reacted with aldimine **3**, and gave the corresponding quinoline **2b** in 84% yield (eq 2).



R	X / mol %	Yield/%	
Ph	5	91 (**2a**)	3 (**1a**)
^{n}Bu	10	84 (**2b**)	<1 (**1b**)

One-pot three-component coupling of benzaldehyde (**5**), aniline (**6**), and phenylacetylene (**4a**) also provided quinoline **2a** in 92% yield (eq 3).



In summary, we have succeeded in copper(I)- and gold(I)-catalyzed synthesis of 2,4-disubstituted quinoline derivatives from *N*-aryl-2-propynylamines. The quinoline derivatives could also be obtained by the reaction of *N*-arylaldimines with terminal acetylenes via the formation of *N*-aryl-2-propynylamines. In the former reactions, the combination of gold(I) chloride and silver triflate was better able to give quinoline derivatives. On the other hand, in the latter reactions, the combination of copper(I) chloride and silver triflate showed a higher efficiency than that of gold(I) chloride and silver triflate.

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10 Results for other catalysts are as follows: CuCl, 15%; AgOTf, 90%; $CuCl_2$, 10%; $Cu(OTf)_2$, 92%; CuCl + $In(OTf)_3$, 94%; $CuCl_2$ + $In(OTf)_3$, 81%; $In(OTf)_3$, 10%; AuCl + AgOTf, 99%; AuCl, 32%; $AuCl_3$ + AgOTf, 98%; $AuCl_3$, 17%; $GaCl_3$, 20%; $InCl_3$, 18%; $PtCl_2$, 39%.

11 Copper-catalyzed synthesis of quinoline derivatives has already been reported. However, the yield of quinolines and efficiency were low. See: ref. 9b.

12 In this reaction, 1,2-dihydroquinoline was not detected.

13 Results for other acceptors are as follows: norbornene, 39%; 3,3-dimethyl-1-butene, 46%; 3-pentanone, 18%; acetophenone, 43%; nonanal, 58%; benzaldehyde, 59%.

14 When O_2 or aq. H_2O_2 was used as an oxidant, the yield of **2a** could not be improved.

15 Benzylphenylamine was obtained in 91% yield.

16 Only a trace amount of quinoline **2f** was formed in the absence of AgOTf.

17 There have been some reports on copper(I)-catalyzed synthesis of 2-propynylamines from aldimines and terminal acetylenes. See: a) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638. b) J. N. Rosa, A. Gil Santos, C. A. M. Afonso, *J. Mol. Catal. A: Chem.* **2004**, *214*, 161. c) M. Benaglia, D. Negri, G. Dell'Anna, *Tetrahedron Lett.* **2004**, *45*, 8705.

18 The combination of gold(I) chloride and silver triflate, which has high ability to catalyze the formation of quinoline **2a** from 2-propynylamine **1a**, showed low ability to catalyze the formation of quinoline **2a** (41%) by the reaction of aldimine **3** with phenylacetylene (**4a**). This result shows that the combination of gold(I) chloride and silver triflate is not effective for the formation of 2-propynylamine **1a** from aldimine **3** and phenylacetylene (**4a**). Results for other catalysts are as follows: $Cu(OTf)_2$, 82%; AgOTf, 61%; CuCl + $In(OTf)_3$, 91%.

19 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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