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Synthesis of Substituted 1,2-Dihydroquinolines and Quinolines from Aromatic Amines and Alkynes by Gold(I)-Catalyzed Tandem Hydroamination–Hydroarylation under Microwave-Assisted Conditions

Xin-Yuan Liu, Pan Ding, Jie-Sheng Huang, and Chi-Ming Che*

Department of Chemistry and Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis, The University of Hong Kong, Pokfulam Road, Hong Kong, People's Republic of China

cmche@hku.hk

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ABSTRACT

A method to efficiently prepare substituted 1,2-dihydroquinolines and quinolines by Au(I)-catalyzed tandem hydroamination–hydroarylation under microwave irradiation was developed. This method requires short reaction time (10–70 min) and has a broad substrate scope.

Compounds containing a partially hydrogenated quinoline moiety are potential therapeutics such as inhibitors for lipid peroxidation, HMG-CoA reductase, and progesterone agonists and antagonists.[1] Many synthetic methods including transition metal catalysis have been developed to generate dihydroquinoline compounds.[2,3] As inter- and intramolecular formation of dihydroquinolines usually requires high temperature and/or prolonged reaction time, and most of the reported catalysts for dihydroquinoline synthesis showed limited scope of substrates and modest selectivity, a mild and efficient protocol for the synthesis of this class of compounds would be highly desirable.

Au(I) and Au(III) complexes have increasingly been used as catalysts for a variety of organic transformations,[4,5] and gold-catalyzed intermolecular hydroamination of alkynes[3c,6]

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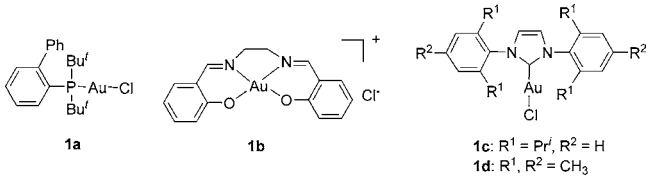
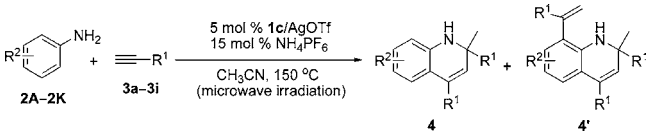
and inter- or intramolecular hydroarylation of alkynes[7] have been reported. Since catalytic dual activation is of interest from the perspective of atom economy, we are interested to explore gold-catalyzed tandem hydroamination−hydroarylation as a possible synthetic strategy for substituted 1,2-dihydroquinolines, particularly under microwave-assisted conditions to shorten the reaction time.[5l]

The gold complexes **1a**,[8] **1b**,[9] **1c**,[10] and **1d**[10] employed in this work were prepared by literature methods. We examined



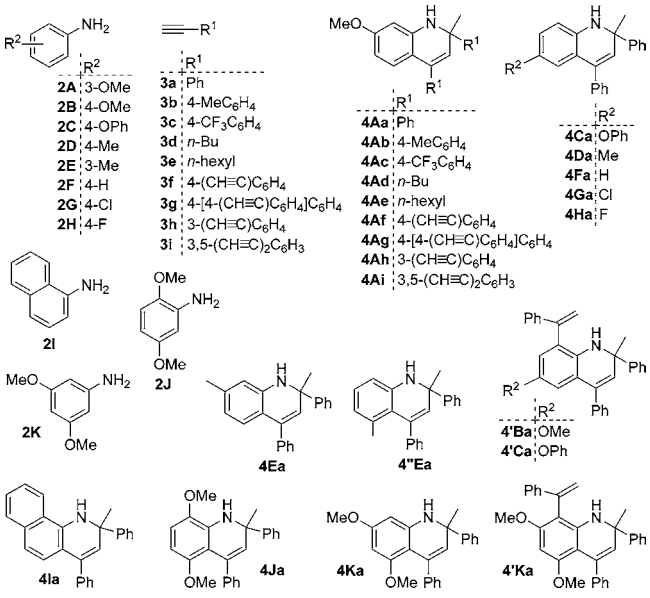
the reaction of *m*-anisidine (**2A**) with phenylacetylene (**3a**) at 80−100 °C in the presence of 5 mol % of these gold catalysts, which gave 1,2-dihydroquinoline derivative **4Aa** in up to 80% yields after 12−24 h (Table S1 in the Supporting Information). Upon microwave irradiation, the reaction time considerably shortened to 25 min, with the best result obtained for the Au(I) catalyst **1c**/AgOTf with CH_3CN as solvent in the presence of additive NH_4PF_6 (Table S2 in the Supporting Information). Under these conditions, **1c**/AgOTf catalyzed the reactions of primary arylamines

Scheme 1



2A−**K** with alkynes **3a**−**i** to give dihydroquinoline derivatives **4** and/or **4′** (Scheme 1) in 42−94% yields (Table 1; a control experiment with $AgOTf/NH_4PF_6$ as catalyst afforded **4Aa** in 2% NMR yield).

Table 1. Gold(I)-Catalyzed Reactions between Primary Arylamines **2A**−**K** and Alkynes under Microwave Irradiation[a]



entry	substrates	product(s)	time (min)/*P* (W)	yield[b] (%)
1	**2A** + **3a**	**4Aa**	25/26	82
2	**2A** + **3b**	**4Ab**	30/25	81
3	**2A** + **3c**	**4Ac**	40/24	73
4	**2A** + **3d**	**4Ad**	40/30	83
5	**2A** + **3e**	**4Ae**	60/26	89
6	**2A** + **3f**	**4Af**	60/40	71
7	**2A** + **3g**	**4Ag**	70/47	42
8	**2A** + **3h**	**4Ah**	60/43	64
9	**2A** + **3i**	**4Ai**	60/28	52
10	**2B** + **3a**	**4′Ba**	35/19	78
11	**2C** + **3a**	**4Ca** + **4′Ca**	45/20	84 (11:10)
12	**2D** + **3a**	**4Da**	40/23	71
13	**2E** + **3a**	**4Ea** + **4″Ea**	40/25	85 (8:7)
14	**2F** + **3a**	**4Fa**	40/26	74
15	**2G** + **3a**	**4Ga**	70/21	62;[c] 71[d]
16	**2H** + **3a**	**4Ha**	70/29	54[c]
17	**2I** + **3a**	**4Ia**	40/21	69[c]
18	**2J** + **3a**	**4Ja**	40/26	65
19	**2K** + **3a**	**4Ka** + **4′Ka**	30/28	94 (27:67)

[a] Reaction conditions: **2** (0.5 mmol), **3** (2.5 mmol), **1c**/AgOTf (0.025 mmol), NH_4PF_6 (0.075 mmol), CH_3CN (1 mL), 150 °C with microwave irradiation. [b] Isolated yield based on arylamine. [c] A 20−40% yield of imine was obtained. [d] **1a**/AgOTf was used as catalyst.

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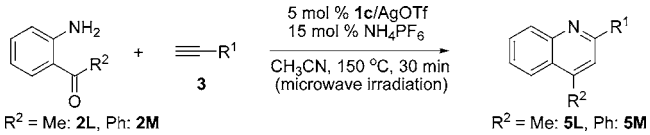
The **1c**/AgOTf-catalyzed reactions of **2A** with monoalkynes **3a**−**e** afforded **4Aa**−**Ae** in 73−89% yields (entries 1−5, Table 1). Interestingly, extension of the reaction to the substrates bearing multiple alkyne groups (**3f**−**i**) gave **4Af**−**Ai** in 42−71% yields (entries 6−9, Table 1); each molecule of these dihydroquinolines features two or four terminal alkyne groups.

Reactions of **3a** with arylamines **2B**−**K** catalyzed by **1c**/AgOTf afforded **4Ca**−**Ka**, together with **4′Ba**, **4′Ca**, **4′′Ea**, and **4′Ka** (entries 10−19, Table 1). *p*-Anisidine (**2B**) was the most reactive, with **4′Ba** formed in 78% yield within 35 min (entry 10). For 4-phenoxyaniline (**2C**), a 11:10 mixture of **4Ca** and **4′Ca** was obtained in a total of 84% yield (entry 11). *p*- and *m*-methyl-substituted anilines reacted with **3a** to give different products: only **4Da** was obtained (in 71% yield) for *p*-toluidine (**2D**, entry 12), but a 8:7 mixture of **4Ea** and **4′′Ea** (in a total of 85% yield) was formed for *m*-toluidine (**2E**, entry 13). In the case of substrate **2G** bearing electron-withdrawing *p*-Cl substituent, the product **4Ga** was obtained in 62% yield, and changing the catalyst to **1a**/AgOTf increased the yield to 71% after reaction for 1 h (entry 15). This contrasts with the formation of similar 1,2-dihydroquinoline derivatives in <5% yields for the arylamines bearing an electron-withdrawing substituent in ruthenium-catalyzed reactions.[3b] In the presence of catalyst **1c**/AgOTf, disubstituted arylamines **2J** and **2K** reacted with **3a** to afford **4Ja** in 65% yield (entry 18) and a 27:67 mixture of **4Ka** and **4′Ka** in a total of 94% yield (entry 19).

Under similar conditions, the **1c**/AgOTf-catalyzed reactions of alkynes **3a**−**c** and **3e** with primary arylamines **2L** and **2M** bearing an *o*-alkylcarbonyl or -arylcarbonyl group produced 2,4-disubstituted quinolines **5L** and **5M** in 63−94% yields within 30 min (entries 1−6, Table 2; a

Table 2. Gold(I)-Catalyzed Two-Component Synthesis of Quinolines under Microwave Irradiation



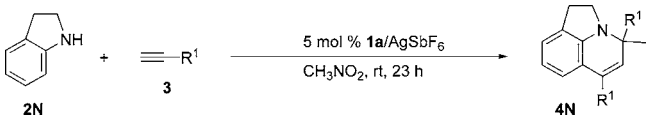
R^2 = Me: **2L**, Ph: **2M** — R^2 = Me: **5L**, Ph: **5M**

entry	R^1	substrates	product	yield (%)
1	Ph	**2L** + **3a**	**5La**	93
2	4-MeC_6H_4	**2L** + **3b**	**5Lb**	94
3	4-$CF_3C_6H_4$	**2L** + **3c**	**5Lc**	83
4	*n*-hexyl	**2L** + **3e**	**5Le**	63
5	Ph	**2M** + **3a**	**5Ma**	89
6	4-MeC_6H_4	**2M** + **3b**	**5Mb**	91
7	4-(CH≡C)C_6H_4	**2L** + **3f**	**5Lf**	81
8	3-(CH≡C)C_6H_4	**2L** + **3h**	**5Lh**	72
9	3,5-$(CH≡C)_2C_6H_3$	**2L** + **3i**	**5Li**	65

control experiment with AgOTf/NH_4PF_6 as catalyst gave **5La** in 4% NMR yield). These reactions are related to the syntheses of 2,4-disubstituted quinolines from the Cu(I)-catalyzed reactions of arylaldehydes, alkynes, and primary arylamines.[11] For the reaction of **2L** with **3a** catalyzed by **1c**/AgOTf, the yield of **5La** remained almost the same upon decreasing catalyst loading from 5 to 2 mol % (Table S3 in the Supporting Information). Note that previous synthesis of **5La** and **5Ma** has considerably lower product yields[12a] or requires a substantially longer reaction time.[12b] For example, the formation of **5Ma** from the $Ru_3(CO)_{12}$-catalyzed reaction of **2M** with **3a** was performed at 150 °C for 12 h.[12b] In view of the potential therapeutic applications,[13] we developed a gram-scale synthesis of **5La** (Scheme S1 in the Supporting Information). It is interesting that the **1c**/AgOTf-catalyzed reactions of **2L** with **3f**, **3h**, and **3i** afforded **5Lf**, **5Lh**, and **5Li**, respectively, each bearing one or two terminal alkyne groups; such compounds, along with **4Af**−**Ai**, are potentially useful for constructing supramolecular architectures[14] and metal−alkynyl optoelectronic materials.[15]

Indoline (**2N**), a secondary arylamine, was also found to react with alkynes in the presence of a Au(I) catalyst. Treatment of **2N** with **3a** using 5 mol % of **1a**/AgOTf in CH_3CN gave **4Na** in 91% yield within 10 min under microwave irradiation (entry 1, Table 3). When the reaction

Table 3. Gold(I)-Catalyzed Reactions between Indoline and Alkynes[a]



2N — **4N**

entry	R^1	substrates	product	yield[b] (%)
1[c]	Ph	**2N** + **3a**	**4Na**	91
2	Ph	**2N** + **3a**	**4Na**	84
3	4-MeC_6H_4	**2N** + **3b**	**4Nb**	81
4	4-$CF_3C_6H_4$	**2N** + **3c**	**4Nc**	95
5	*n*-Bu	**2N** + **3d**	**4Nd**	58
6	*n*-hexyl	**2N** + **3e**	**4Ne**	63
7	4-$MeOC_6H_4$	**2N** + **3j**	**4Nj**	68
8	4-FC_6H_4	**2N** + **3k**	**4Nk**	86

[a] Reaction conditions: **2N** (0.5 mmol), **3** (2.5 mmol), CH_3NO_2 (1 mL). [b] Isolated yield based on **2N**. [c] Reaction performed in CH_3CN with catalyst **1a**/AgOTf under microwave irradiation for 10 min.

was performed at room temperature, a much longer reaction time of 23 h was required and the best result was obtained by using the solvent CH_3NO_2 and catalyst **1a**/$AgSbF_6$. Under these conditions, reactions of **2N** with **3a**−**e**, **3j**, and **3k**

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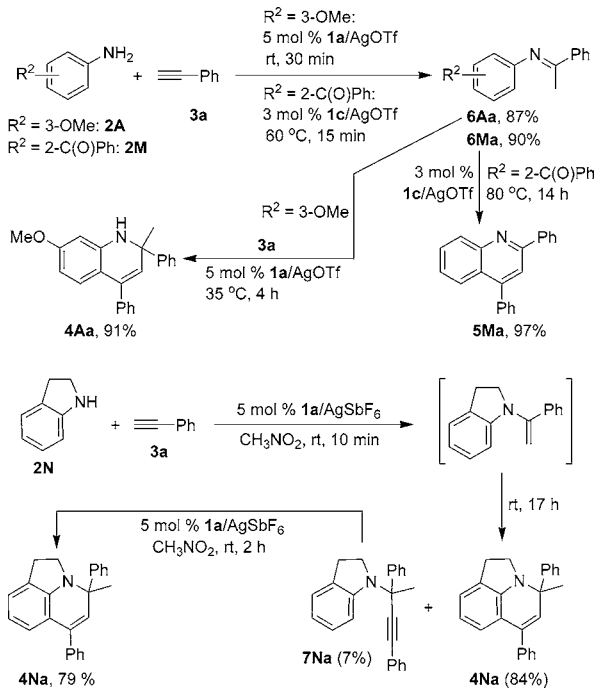
afforded **4Na**−**Ne**, **4Nj**, and **4Nk**, respectively, in 58−95% yields (entries 2−8, Table 3). A similar yield of **4Na** or **4Nb** was previously obtained from $Ru_3(CO)_{12}$-catalyzed reactions at 95 °C for 16 h.[3a]

To provide insight into the mechanism of the Au(I)-catalyzed transformations, we examined the **1a**/AgOTf-catalyzed reaction of **2A** with **3a** at room temperature and the **1c**/AgOTf-catalyzed reaction of **2M** with **3a** at 60 °C, which afforded ketimine **6Aa** in 87% yield after 30 min and **6Ma** in 90% yield after 15 min, respectively (Scheme 2).

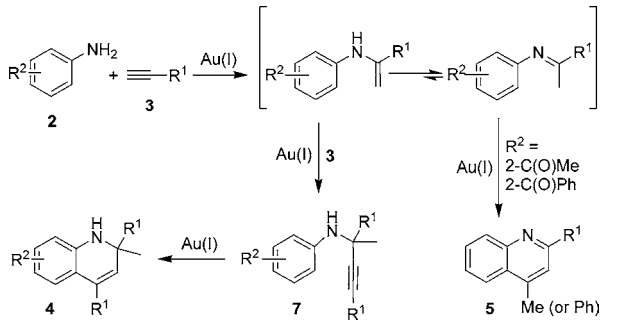
Scheme 2



Subsequent reaction of **6Aa** with **3a** catalyzed by **1a**/AgOTf at 35 °C for 4 h gave **4Aa** in 91% yield, whereas **6Ma** was converted to **5Ma** in 97% yield upon treatment with catalyst **1c**/AgOTf at 80 °C for 14 h. Monitoring the **1a**/$AgSbF_6$-catalyzed reaction of **2N** with **3a** at room temperature revealed the formation of an enamine intermediate (characterized by the vinyl proton resonances at δ 5.37 and 5.24 ppm) within 10 min, which was converted to **4Na** and propargylamine **7Na** in 84% and 7% yields, respectively, after 17 h. Treatment of **7Na** with **1a**/$AgSbF_6$ in CH_3NO_2 at room temperature for 2 h afforded **4Na** in 79% yield (Scheme 2).

On the basis of these observations and by considering previous works on gold-catalyzed hydroamination reactions,[6] a reaction mechanism for the formation of **4** and **5** from the Au(I)-catalyzed reactions of **2** with **3** was proposed (Scheme 3), which involves hydroamination of alkynes to generate

Scheme 3



an enamine intermediate in tautomerization with a ketimine, and reaction of the enamine or ketimine intermediate with alkynes[3c] to form a propargylamine intermediate,[5k,16] followed by an intramolecular hydroarylation to produce **4**.[7] The ketimines generated from **2L** and **2M** could undergo a condensation/annulation reaction to give **5**.

In conclusion, we have developed a method to efficiently prepare substituted 1,2-dihydroquinolines and quinolines by Au(I)-catalyzed tandem hydroamination−hydroarylation under microwave irradiation. This method features a short reaction time and a broad substrate scope, including the substrates bearing multiple alkyne groups.

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Supporting Information Available: Experimental procedures, product characterizations, Tables S1−S3 giving catalyst activity data, and Scheme S1 showing the gram-scale synthesis of quinoline derivative **5La**. This material is available free of charge via the Internet at http://pubs.acs.org.

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