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Silver-catalyzed cascade reaction of *o*-aminoaryl compounds with alkynes: an aniline mediated synthesis of 2-substituted quinolines

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ABSTRACT

An efficient silver-catalyzed, aniline mediated cascade hydroamination/cycloaddition of *o*-aminoaryl compounds including *o*-aminoaryl aldehydes, *o*-aminoaryl ketones with alkynes for the synthesis of 2- or 2,4-substituted quinolines is reported. The reactions proceed with high regioselectivity to afford mono- or disubstituted quinoline derivatives in good to high yields using AgOTf as the catalyst in the air.

Quinoline skeletons are important substructures in a large number of natural or designed products with interesting biological activities.[1] The quinoline ring system occurs widely in drugs with activities, such as antibacterial, antiinflammatory, antifungal and analgesic properties.[1c,2] They are also useful synthetic building blocks in organic chemistry.[3] The classical methods for the synthesis of quinolines include Skraup, Doebner-von Miller, Friedlander and Combes reactions, etc.[4–7] Among them, Friedlander reaction is one of the most straightforward methods and excellent works have been disclosed.[8] The reported procedures usually involve acid- or base-catalyzed condensation between a 2-aminoaryl ketone or an aldehyde and a carbonyl compound possessing a reactive α-methylene group. Recently, reports concerning transition metal mediated synthesis of quinolines have also appeared,[9] many transition metals, such as rhodium,[9a,b] iron,[9c] zinc,[8b] iridium,[9d] copper,[9e] and ruthenium[9f,g] were used. Although these methods are effective, most of them suffer from strong acid or base conditions, high reaction temperatures. Furthermore, for most of these processes one of the reactants was limited to the carbonyl compound bearing a reactive α-methylene group. Therefore, the development of new procedures with novel substrate scope is in great demand.[10] Recently, Che and coworkers reported an efficient synthesis of 2,4-disubstituted quinolines from the reaction of *o*-aminoaryl ketones with terminal alkynes using special gold complexes.[10a] However, *o*-aminoaryl aldehydes were not applicable in the reaction, possibly due to their readily self-condensation reactions. We previously reported the Cu-catalyzed synthesis of benzofurans by the three-component reaction of salicylaldehyde, alkyne, and amines.[11] We envisioned that by changing the salicylaldehyde to *o*-aminoaryl aldehyde, the 3-aminoindole or disubstituted 4-aminodihydroquinoline would be formed (Scheme 1, (Eq. 1)). Interestingly, only 2-substituted quinolines[12] were obtained (Scheme 1, (Eq. 2)). Herein, we report a regioselective synthesis of 2 or 2,4-substituted quinolines from the reaction of *o*-aminoaryl aldehyde or *o*-aminoarylketone, alkyne and aniline catalyzed by simple silver salt.

We started our investigation with the reaction of 2-aminobenzaldehyde (**1a**), dibenzylamine (**4a**), and phenylacetylene (**2a**) using 20 mol % CuI as the catalyst in the presence of K_2CO_3, Bu_4NBr in toluene at 110 °C as reported previously,[11] only the dimmerization of phenyacetylene was detected (Table 1, entry 1). Then we carried out the reactions without the addition of K_2CO_3 and Bu_4NBr. When the catalyst was changed to 2 mol % of $NaAuCl_4{\cdot}2H_2O$, no reaction took place (Table 1, entry 2). It was interesting to note that in the absence of a secondary amine **4a**, 2-aminobenzaldehyde reacted with phenylacetylene to give 2-phenyl quinoline **3a** in 23% yield. Five mole percent of $NaAuCl_4{\cdot}2H_2O$ increased the product yield to 47% (Table 1, entry 4). Surprisingly, the addition of a primary amine of aniline remarkably improved the product yield to 63% (Table 1, entry 5). Other acids, such as $BF_3{\cdot}Et_2O$ and TfOH gave no desired product. We were happy to see when the catalyst was changed to AgOTf, the reaction was completed in 3 h, and the desired quinoline derivative **3a** was obtained in 78% isolated yield (Table 1, entry 9). Control experiments without the addition of AgOTf or aniline resulted in no or trace amount of the desired

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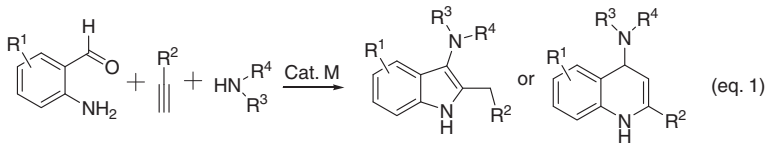
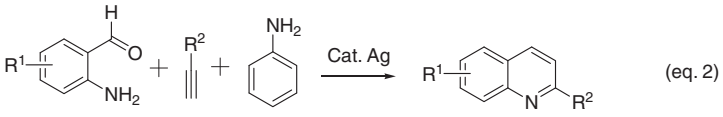
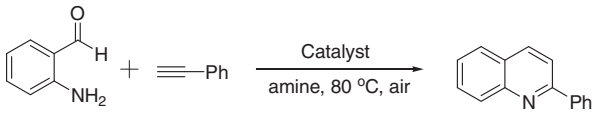




Cascade hydroamination/cycloaddition reactions

Scheme 1. The reaction of *o*-aminoaryl aldehyde, alkyne and amine.

Table 1
Optimization of reaction conditions for the synthesis of **3a**



1a **2a** **3a**

Entry	Catalyst (mol %)	Amine (equiv)	Solvent	Yield[a]
1	CuI (20)	Dibenzylamine (1.0)	Toluene	—[b,c]
2	$NaAuCl_4{\cdot}2H_2O$ (2)	Dibenzylamine (2.0)	DCE	—[c]
3	$NaAuCl_4{\cdot}2H_2O$ (2)	—	DCE	23%
4	$NaAuCl_4{\cdot}2H_2O$ (5)	—	DCE	47%
5	$NaAuCl_4{\cdot}2H_2O$ (5)	Aniline (4)	DCE	63%
6	$BF_3{\cdot}Et_2O$ (5)	Aniline (4)	DCE	—[c]
7	TfOH (5)	Aniline (4)	DCE	—[c]
8	AgOTf (2)	Aniline (4)	DCE	51%
9	AgOTf (5)	Aniline (4)	DCE	78%
10	AgOTf (5)	Aniline (4)	DCE	39%[d]
11	AgOTf (5)	Aniline (4)	DCE	57%[e]
12	AgOTf (5)	Aniline (4)	Chlorobenzene	63%
13	AgOTf (5)	Aniline (4)	Toluene	37%
14	AgOTf (5)	Aniline (4)	CH_3CN	24%
15	AgOTf (5)	Aniline (4)	1.4-Dioxane	61
16	AgOTf (5)	*p*-Toluidine (4)	DCE	73
17	AgOTf (5)	Butan-1-amine (4)	DCE	NR[f]
18	—	Aniline (4)	DCE	—[c]
19	AgOTf	—	DCE	Trace

[a] Isolated yield; unless otherwise noted, all the reactions were carried out with the ratio of **1a**:**2a**:**4b** = 1:3:4.
[b] 1 equiv of K_2CO_3 and 1 equiv of Bu_4NBr were added.
[c] No desired product.
[d] The ratio of **1a**:**2a**:**4b** = 1:1.5:4.
[e] The ratio of **1a**:**2a**:**4b** = 1:3:2.
[f] NR = no reaction.

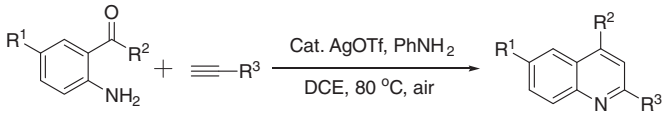
product (Table 1, entries 18 and 19). Less AgOTf (2 mol %) gave only 51% yield (Table 1, entry 8). Decreasing the amount of **2a** to 1.5 equiv also resulted in much lower yield (Table 1, entry 10). When *p*-toluidine was used, the product yield was slightly lower than that of aniline (Table 1, entry 16). However, butan-1-amine gave no desired product (Table 1, entry 17). Switching to other solvents such as chlorobenzene, acetonitrile or 1,4-dioxane afforded much lower yields (Table 1, entries 12–15). It was clear that the optimized reaction condition was to use 5 mol % of AgOTf as the catalyst with aniline as the additive under an air atmosphere using dichloroethane as the solvent.

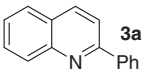
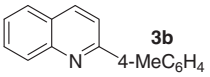
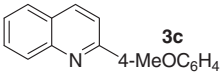
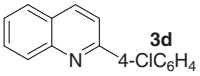
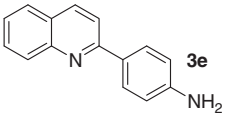
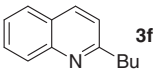
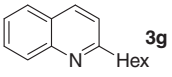
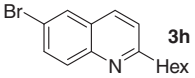
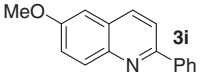
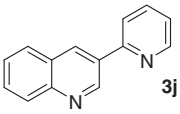
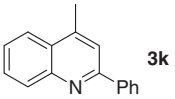
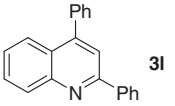
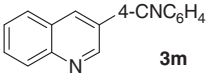
Having established an effective catalytic system for the synthesis of quinolines, we next examined the reaction of a variety of *o*-aminoaldehydes and terminal alkynes to explore the scope of the cascade hydroamination-cyclization reactions under the optimized conditions. The representative results are shown in Table 2. The reaction was applicable to various terminal alkynes and *o*-aminoaldehydes. Alkyne **2b** with an electron-donating (–*p*-Me) aryl group reacted smoothly with **1a** to give the quinoline **3b** in 74% yield (Table 2, entry 2), the electron-donating (–*p*-OMe) aryl group alkyne **2c** afforded **3c** in 77% yield (Table 2, entry 3). While **2d** with electron-withdrawing (–*p*-Cl) aryl group gave rise to the corresponding **3d** in 78% yield, along with 78% of aniline recovered (Table 2, entry 4). When 4-aminophenylacetylene (**2e)** was employed, the corresponding quinoline was produced in 84% yield, in which the NH_2 group was well tolerated during the reaction (Table 2, entry 5). Moreover, aliphatic acetylenes, such as 1-hexyne (**2f**) and 1-octyne (**2g**) were also compatible under the reaction conditions, furnishing the desired quinolines in good yields, however, 10 mol % of AgOTf and longer reaction time were required (Table 2, entries 6 and 7). It is worthy to note that when 2-pyridyl acetylene (**2h**) was used, a 3-pyridyl substituted quinoline **3j** was produced in high yield (Table 2, entry 10). It indicated that the regioselectivity of the hydroamination of 2-pyridyl acetylene is different from that of the other alkynes. Similarly, **2i** with a strong electron-withdrawing (–*p*-CN) aryl group gave rise to the corresponding 3-substituted quinoline **3m**[14] in 67% yield (Table 2, entry 13).

Substrate scope of the reaction could be extended to substituted *o*-aminoarylaldehydes and *o*-aminoaryl ketones, the desired quinolines were obtained in good yields. When 5-bromo-2-aminoaldehyde (**1b**) was used, the reaction was completed cleanly with **2g** to afford **3h** in 81% yield (Table 2, entry 8). 5-Methoxy-2-aminoaldehyde (**1c**) furnished **3i** in 66% yield (Table 2, entry 9), in which both -Br and -OMe are well tolerated, it offers the possibility for further diversification of the quinoline moiety. *o*-Aminoaryl ketone with a methyl group, namely 1-(2-aminophenyl)ethanone (**1d**) reacted with phenylacetylene under the optimal reaction conditions to give the desired 4-methyl substituted quinoline **3k** in moderated yield (Table 2, entry 11). Similarly, *o*-aminoaryl ketone bearing a phenyl group furnished the corresponding 4-phenyl substituted quinoline **3l** in 69% yield (Table 2, entry 12). It should be noted that when internal alkynes such as diphenylacetylene was treated with **1a** under the optimized reaction conditions, no desired quinoline was observed, only the condensation reaction between **1a** and aniline took place.

To view the insight of the interesting quinoline forming reaction, we first carried out the reaction of 2-aminobenzaldehyde (**1a**) with aniline (**4b**) under the optimal conditions for 3 h, then phenylacetylene (**2a**) was added to the reaction mixture, no desired product could be observed (Eq. 3). This result indicated that

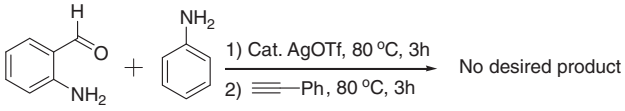
Table 2
Synthesis of quinolines from the reaction of *o*-aminoarylaldehydes, terminal alkynes and aniline



Entry	*o*-Aminoarylaldehyde	Alkyne	Product	Yield[a] (%)
1	**1a**: $R^1 = R^2 = H$	**2a**: R^3 = Ph	 **3a**	78
2	**1a**	**2b**: R^3 = 4-MeC_6H_4	 **3b**	74
3	**1a**	**2c**: R^3 = 4-$MeOC_6H_4$	 **3c**	77
4	**1a**	**2d**: R^3 = 4-ClC_6H_4	 **3d**	78[b]
5	**1a**	**2e**: R^3 = 4-$NH_2C_6H_4$	 **3e**	84
6	**1a**	**2f**: R^3 = Bu	 **3f**	72[c]
7	**1a**	**2g**: R^3 = Hex	 **3g**	75[c]
8	**1b**: R^1 = Br, R^2 = H	**2g**	 **3h**	81[c]
9	**1c**: R^1 = OMe, R^2 = Me	**2a**	 **3i**	66
10	**1a**	**2h**: R^3 = 2-Pyridyl	 **3j**	83
11	**1d**: R^1 = H, R^2 = Me	**2a**	 **3k**	55[d]
12	**1e**: R^1 = H, R^2 = Ph	**2a**	 **3l**	69[d]
13	**1a**	**2i**: R^3 = 4-CNC_6H_4	 **3m**	67

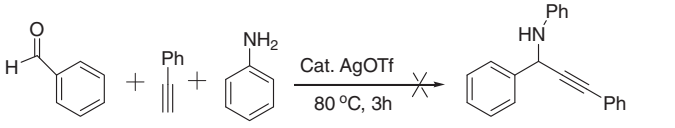
[a] Isolated yield.
[b] Along with 78% of aniline recovered.
[c] 10 mol % AgOTf was used and the reaction time was 6 h.
[d] The reaction time was 36 h.

the quinoline formation through the condensation of **1a** and **4b** could be ruled out.



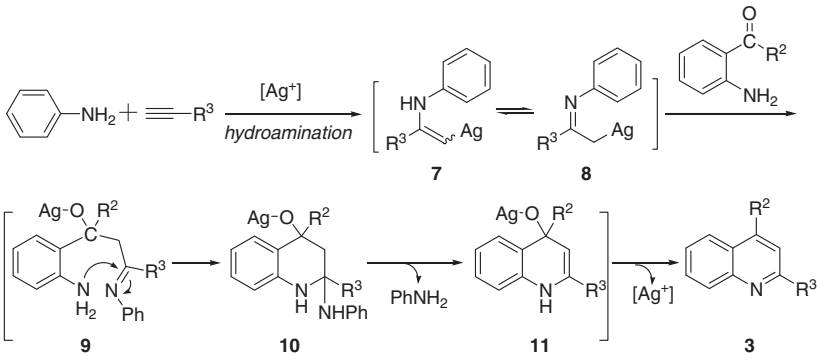
(3)

Another possible pathway involving the three-component reaction of **1a**, **2a**, and **4b** to give propargylic amine, which triggers cycloaddition/aromatization to form quinoline **3**, is also not the case. Because the reaction of benzaldehyde, **2a**, and **4b** under the standard conditions did not afford the corresponding propargylic amine (Eq. 4).

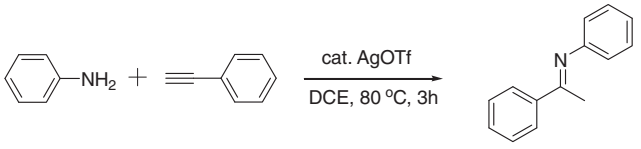


(4)

When aniline was treated with phenylacetylene (**2a**) without the addition of **1a** under the optimal reaction conditions, the hydroamination product **6** was obtained in 24% yield after hydrolysis with most of the starting materials remaining (Eq. 5).



Scheme 2. A proposed reaction mechanism.



(5)

Based on the above observations and the reported results of the hydroamination reactions,[10,13] a plausible reaction mechanism was proposed (Scheme 2), which involves hydroamination of alkynes to produce intermediate **7** or **8**, and the reaction of **8** with *o*-aminoaryl ketone **1** to form intermediate **9**. Then intramolecular cycloaddition followed by aromatization gave the desired quinoline **3**. We tried the reaction at lower temperature in order to 'observe' intermediate **9**. However, no information about **9** could be obtained at the current stage. It seems that the transformation of **9** to the final quinoline is fast.

In summary, we have reported an efficient silver-catalyzed cascade hydroamination–cyclization reactions of acetylenes and a variety of *o*-aminoaryl compounds, such as *o*-aminoarylaldehydes and *o*-aminoaryl ketones with the assistance of aniline. The reactions proceed to afford 2- or 2,4-substitued quinoline derivatives in good to high yields using AgOTf as the catalyst under mild reaction conditions.

Acknowledgments

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Supplementary data

Supplementary data (experimental details and spectroscopic characterization of all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.102.

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