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A Silver-Catalyzed Domino Route toward 1,2-Dihydroquinoline Derivatives from Simple Anilines and Alkynes

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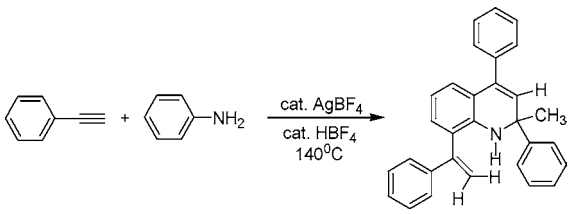
ABSTRACT



A silver-catalyzed domino reaction of simple anilines and alkynes generates 1,2-dihydroquinoline derivatives efficiently.

The partially hydrogenated quinoline moiety bearing different functional groups is an important building block in various natural products. It has exhibited a broad range of biological activities and potential pharmaceutical applications.[1] Typical biological reactivities of such compounds include psychotropic,[2] anti-allergenic[3] anti-inflammatory,[4] and estrogenic activities.[5] Since Povarov's pioneering work in the mid 1960s, Lewis acid catalysis toward tetrahydroquinoline derivatives has been extensively studied.[6] Very recently, we reported an indium trichloride catalyzed 2:1 coupling of dihydropyran or dihydrofuran with aniline derivatives to provide tetrahydroquinoline derivatives.[7] On the other hand, Skraup and Bischler−Napieralski reactions have been commonly utilized in the synthesis of dihydroquinolines; these involve the use of aniline and a ketone or an intramolecular condensation of an aromatic amide.[8]

For the synthesis of dihydroquinoline derivatives, Taylor and co-workers reported a Diels−Alder intramolecular addition of 1,2,4-triazines.[9] Arduini and co-workers reported

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a synthesis via a reaction between lithium anilides and phenylacetylene with a stoichiometric amount of tin(IV) chloride to yield 2,4-diphenyl-2-methyl-1,2-dihydroquinoline;[10] Rana developed the synthesis of dihydroquinolines by the reaction of anilines with alkyl vinyl ketones in the presence of indium trichloride under microwave irradiation.[11] Several examples of dihydroquinoline synthesis via transition metal catalysis have also been reported very recently. Nakagawa and co-workers described a method that used ruthenium-catalyzed ring-closing metathesis for synthesizing substituted quinolines;[12] Ward and co-workers reported a copper-catalyzed coupling of aniline with propargyl chloride to generate 2,2-disubstitued-1,2-dihydroquinoline via an interesting intramolecular hydroarylation of the alkyne.[13] However, the substrate availability, cost, stoichiometric amount of additives, and functional group tolerance are some limitations of the current methods for dihydroquinoline synthesis. Therefore, a simple and novel method for synthesizing 1,2-dihydroquinoline, especially polysubstituted ones, is highly desirable and has practical benefits.

Herein we wish to present the first example of a silver-catalyzed regioselective domino reaction using simple anilines and alkynes, which are easily available from commercial vendors, to give synthetically useful polysubstituted 1,2-dihydroquinoline derivatives efficiently. The study was based on both the Lewis acidity and the transition metal character of the silver catalyst. Furthermore, as a general objective toward the goal of green chemistry and atom-economical synthesis, the process has been carried out under solvent-free conditions.[14]

As a preliminary study, we explored the hydroamination of unactivated alkynes by anilines with a gold/silver catalyst system. Amines were obtained in high yields via a gold- and silver-catalyzed hydroamination of alkynes followed by reduction (Scheme 1). The results of this sequential hydroamination-reduction are summarized in Table 1.[15] Subsequently, we examined the catalytic activities of AgOTf alone as the catalyst for this transformation. As we expected, AgOTf catalysis for the hydroamination of alkynes is less effective than the Au-catalyzed one under the same reaction condititons. To our surprise, when an excess amount of alkyne was used, the reaction of phenylacetylene and aniline generated products **4a** and **5a** in 50% and 20% yield, respectively, at 140 °C under solo $AgBF_4$ catalyst. Aliphatic alkynes could only afford **4a**-type product.

Scheme 1

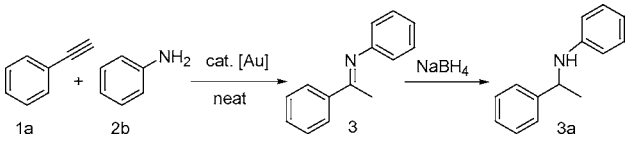
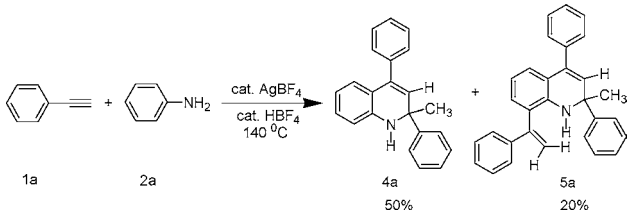


Table 1. Hydroamination of Unactivated Alkynes

entry	alkyne	amine	product	yield[a]
1[b]	1a	2a	3a	88%
2[c]	1a	2b	3b	52%
3[c]	1a	2c	3c	60%
4[d]	1a	2d	3d	50%
5[c]	1b	2a	3e	87%
6[c]	1c	2a	3f	73%
7[c]	1d	2a	3g	73%
8[c]	1d	2d	3h	58%
9[c]	1d	2e	3i	40%

[a] Isolated yields were reported; all reactions were carried out with 1 mmol alkyne and 1.5 mmol amine. [b] 5% $AuCl_3$, room temperature. [c] 5% $AuCl_3$/15% AgOTf, 60 °C. [d] Same as *c*, 110 °C.

Scheme 2



Interestingly, Au catalyst alone did not provide these products. After subsequent optimization of the reaction conditions (Supporting Information), compound **5** was

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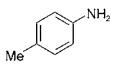
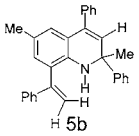
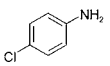
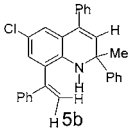
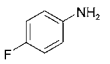
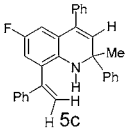
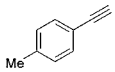
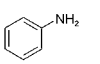
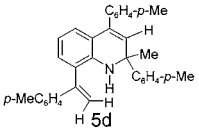
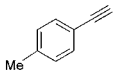
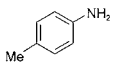
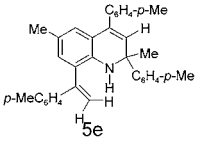
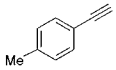
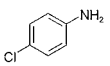
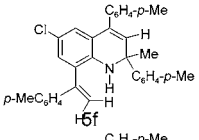
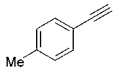
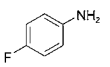
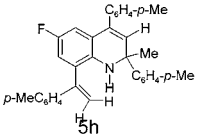
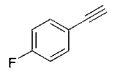
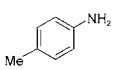
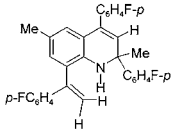
Table 2. Silver-Catalyzed Tandem Reaction of Alkynes and Anilines[a]

entry	alkyne	amine	product	yield (%)[d]
1[b]	 1a	 2b	 5b	79
2[b]	 1a	 2f	 5b	85
3[b]	 1a	 2d	 5c	66
4[b]	 1c	 2a	 5d	60
5[c]	 1c	 2b	 5e	88
6[c]	 1c	 2f	 5f	73
7[b]	 1c	 2d	 5h	70
8[b]	 1e	 2b	 5i	69

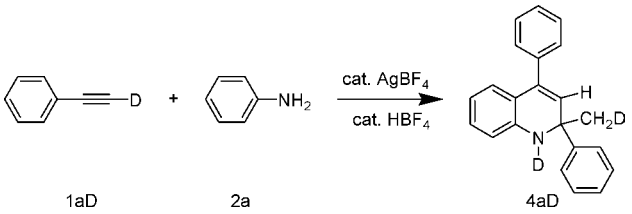
[a] All reactions were carried out by employing aniline (1.0 mmol), alkyne (4.0 mmol), $AgBF_4$ (0,05 mmol), HBF_4 (0.07 mmol, 54% solution in diethyl ether). and $BF_3{\cdot}Et_2O$(0.08 mmol). [b] Stirred at 190 °C. [c] Stirred at 160 °C. [d] Isolated yields.

obtained in good yield using the combined $AgBF_4/HBF_4$ system. Various polysubstituted dihydroquinoline products were obtained from alkynes and aniline via this reaction, and the results are summarized in Table 2.

Good to excellent yields were obtained in almost all cases. The catalyst system is quite insensitive to the electronic effect of both alkynes and anilines. More electron-rich substrates (compare entries **5** and **6**) provided the product in a slightly higher yield.

To investigate the possible mechanism of the reaction, an isotope experiment was performed using deuterium-labeled phenylcetylene with aniline at 140 °C catalyzed by $AgBF_4/HBF_4$ (Scheme 3).[16] Compound **4aD** was observed as the

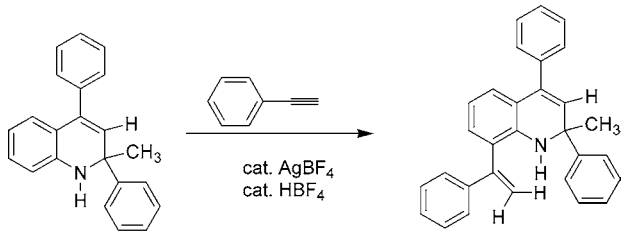
Scheme 3



1aD 2a 4aD

major product, which indicated a possible step involving the addition of phenylacetylene to the ketimine intermediates.[17] As the corresponding propargylamine intermediates have not been isolated or identified at the current stage, we could not rule out the possibility of a 6e-electrocyclic process, which will give a similar product. However, since only product **4aD** was observed in the model study (in Scheme **3**), the latter 6e-electrocyclic process seems unlikely. To gain further insight into the reaction mechanism, 1,2-dihydro-2-methyl-2,4-diphenylquinoline (**4a**) reacted directly with phenylacetylene under the same conditions. Compound **5a** was isolated in 62% yield, which suggested a highly regioselective hydroarylation step during the reaction process.[18] On the basis of these experimental results, we tentatively propose a

Scheme 4



4a 62% 5a

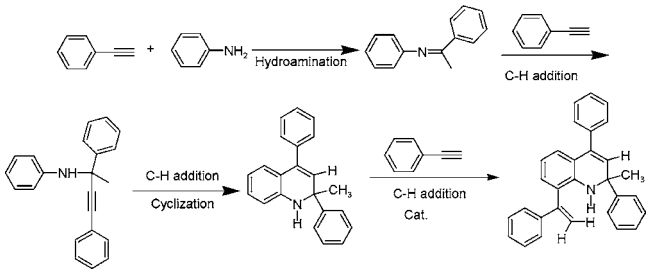
(15) For recent examples of the hydroamination of alkynes, see: (a) Heutling, A.; Pohlki, F.; Doye, S. *Chem. Eur. J.* **2004**, *10*, 3059 and references therein. (b) Illack, A.; Jiao, H.; Castro, I. G.; Hartung, C. G.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2409. (c) Pohlki, F.; Bytschkov, I.; Siebeneicher, H.; Heutling, A.; Koenig, W. A.; Doye, S. *Eur. J. Org. Chem.* **2004**, 1967. (d) Anderson, L. L.; Arnold, J.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 2519. (e) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (f) Lutete, L. M.; Kadaoto, I.; Yammaoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622. (g) Li, Y.; Shi, Y.; Odom, A. L. *J. Am. Chem. Soc.* **2004**, *126*, 1794. For early transition metal/lanthanide catalyzed hydroamination, see: (h) Bürgstein, M. R.; Berberich, H.; Roesky, P. W. *Chem. Eur. J.* **2001**, *7*, 3078. (i) Douglass, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10221. (j) Hong, S.; Marks, T. J. *J. Am. Chem. Soc.* **2002**, *124*, 7886. For Ag- and Au-catalyzed hydroamination, see: (k) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349. (l) Robinson, R. S.; Dovey, M. C.; Gravestock, D. *Eur. J. Org. Chem.* **2005**, 505. (m) Robinson, R. S.; Dovey, M. C.; Gravestock, D. *Tetrahedron Lett.* **2004**, *45*, 6787.

(16) To avoid deuterium and hydrogen exchange during the prolonged reaction time, this model study was carried out under microwave irradiation at 140 °C with 100 W operating power for 20 min.

(17) (a) Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473. (b) Li, Z.; Wei, C.; Chen, L.; Varma, R. S.; Li, C.-J. *Tetrahedron Lett.* **2004**, *45*, 2443.

(18) 1,2-Dihydro-2-methyl-2,4-diphenylquinoline is not stable under the current reaction conditions, and the yield is lower than starting from aniline and phenylacetylene directly.

Scheme 5



domino process with three different types of reactions to form the dihydroquinoline core, which include the formation of ketimine, a ketimine addition to form a propargylamine intermediate, and an intramolecular hydroarylation. Then the dihydroquinoline intermediate undergoes a neighboring-group-directed hydroarylation to give the final product.[19]

In summary, we have developed a novel method to generate polysubstituted 1,2-dihydroquinoline derivatives by a one-pot domino process with high regioselectivity using a silver catalyst. Hydroamination, alkyne addition, intramolecular hydroarylation, and hydroarylation of a third molecule of alkyne could be accomplished in a one-pot process with 100% atom economy.[14] The scope, mechanism, and synthetic applications of the reaction are currently under investigation.

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

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