

Gold(III)-Catalyzed Double Hydroamination of *o*-Alkynylaniline with Terminal Alkynes Leading to *N*-Vinylindoles

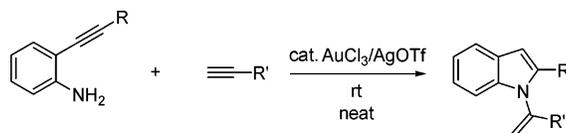
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ABSTRACT



A highly efficient double-hydroamination reaction of *o*-alkynylanilines with terminal alkynes leading to *N*-alkenylindoles was developed by using gold(III) as a catalyst under neat conditions.

Indoles are important chemicals that exhibit a wide range of biological activities.¹ Many naturally occurring compounds contain indole as a key structural motif. Because of the wide application of indoles in pharmaceutical research, the development of efficient methods for their synthesis has continuously attracted the attentions of many chemists.

Among the various synthetic strategies, catalytic transformations by using transition-metal catalysts is one of the modern approaches for forming indoles.^{1,2} In particular, the use of functionalized *o*-alkynylaniline derivatives as the starting materials are some of the most efficient approaches.³

Stille reported the palladium(II)-catalyzed intramolecular cyclization of 2-alkynylanilines to produce 2-substituted indoles in high yield.^{3d} Cacchi and co-workers reported a regioselective synthesis of 3-allylindoles via the palladium-catalyzed cyclization of *o*-alkynyltrifluoroacetanilides with allyl esters.⁴ Knochel reported the synthesis of polyfunctionalized indoles mediated by 1–4 equiv of cesium and potassium bases (such as CsO-*t*-Bu, KO-*t*-Bu, and KH) in *N*-methylpyrrolidinone.⁵ Hiroya and co-workers developed an efficient Cu(II)-catalyzed indole formation and applied the method to natural product syntheses.⁶ Arcadi and co-workers reported a synthesis via a reaction of *o*-alkynylaniline and α,β -enones to form *C*-3-alkylindoles catalyzed by gold catalyst.⁷ Yamamoto and co-workers reported that

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in the presence of certain nucleophiles, such as allyl carbonate and alcohol, tandem cyclization of 2-alkynylaniline proceeded successfully to give the nucleophile incorporated indoles.⁸

On the other hand, *N*-vinylindole compounds have been shown to serve as monomers for the synthesis of poly(*N*-vinylindoles),⁹ which can be used as semiconductors and photosensitizers. However, so far, only a few methods for the synthesis of *N*-vinylindoles have been described.¹⁰ These procedures are rather limited in scope and selectivity.

Recently, we reported a domino reaction of unactivated alkyne and aniline to generate 1,2-dihydroquinolines efficiently catalyzed by AgBF₄.¹¹ In addition, we also found that *o*-alkynylaryl aldehyde reacted with terminal alkynes to form 1-alkynyl-1*H*-isochromenes in water catalyzed by Me₃PAuCl.¹² Herein, we wish to report an efficient double hydroamination of *o*-alkynylaniline with terminal alkynes to form *N*-vinylindole compounds catalyzed by gold(III) under neat conditions.

At the beginning of this study, we found that the double-hydroamination product can be formed in 40% yield by using Cu(OTf)₂ as a catalyst under microwave conditions at 100 °C for 20 min (Table 1, entry 1). Subsequently, it was found

Table 1. Lewis Acid Catalyzed Hydroamination of 2-(Phenylethynyl)aniline and Phenylacetylene^a

entry	cat.	<i>T</i> (°C)	yield ^b (%)
1	Cu(OTf) ₂	100	40
2	Cu(OTf) ₂	60	53
3	Cu(OTf)	60	63
4	AgOTf	60	62
5	AgBF ₄	60	59
6	AuCl ₃	60	73
7	AuCl ₃ /AgOTf	rt	88
8	In(OTf) ₃	rt	no convn
9	Y(OTf) ₃	rt	no convn
10	Sn(OTf) ₂	rt	no convn

^a Conditions: **1a** (0.2 mmol), **1b** (0.4 mmol), rt, N₂. Reaction time was 2 h unless otherwise noted. ^b Yields were determined by ¹H NMR with 0.2 mmol of nitromethane as an internal standard (no convn = no conversion). ^c Reaction time was 20 min under microwave conditions.

that the best conditions for copper and silver catalysts are at 60 °C (entries 2–5). After further optimizations, the desired product can be obtained in 88% yield at room temperature without any solvent in the presence of AuCl₃/AgOTf (5 mol

Table 2. Gold(III)-Catalyzed Double-Hydroamination of *o*-Alkynylaniline and Terminal Alkynes^a

entry	aniline	alkyne	product	yield(%) ^b
1	1a	1b	1c	82
2	1a	2b	2c	79
3	1a	3b	3c	75
4	1a	4b	4c	69
5	1a	5b	5c	80
6	1a	6b	6c	25
7	1a	7b	7c 10%, 7d 17%	
8	1a	8b	8c 11%, 8d 22%	
9	2a	1b	9c	50
10	2a	2b	10c	61
11	2a	3b	11c	50
12	2a	4b	12c	61
13	3a	1b	13c	53
14	3a	2b	14c	50
15	3a	3b	15c	42
16	3a	4b	16c	56
17	4a	4b	17c	67

^a Reaction conditions: 2-alkynylaniline (0.2 mmol), terminal alkyne (0.4 mmol), AuCl₃ (5 mol %), AgOTf (15 mol %), rt, 3 h, N₂. ^b Isolated yield.

%/15 mol %) (entry 7). Other catalysts such as In(OTf)₃, Y(OTf)₃, and Sn(OTf)₂ were found to be ineffective in this

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reaction (entries 8–10). Different solvents were also examined, and the best results were obtained without using any solvent.

Subsequently, various *o*-alkynylanilines were reacted with terminal alkynes under the standard reaction conditions (Table 2). With 2-(phenylethynyl)aniline, both electron-rich and electron-poor arylacetylenes provided excellent yields of the desired products (entries 1–5). Aliphatic alkyl- and alkenylalkynes appeared less reactive (entries 6–8). On the other hand, the reactivities of alkyl- and alkenyl-substituted acetylenic anilines were similar (entries 9–17) and were lower than those of phenyl-substituted acetylenic anilines. The molecular structure of **4c** was confirmed by its X-ray single-crystal diffraction (Figure 1). The presence of a bulky

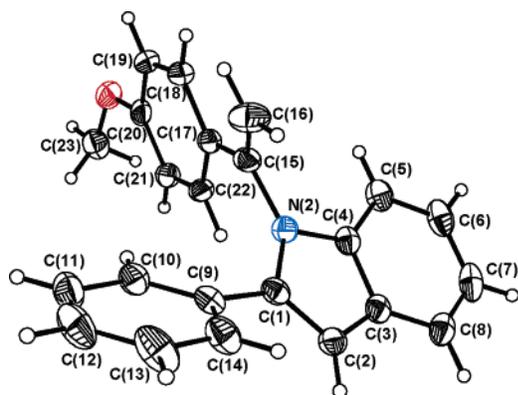


Figure 1. ORTEP diagram of **4c**. Important bond distances include: C(1)–C(2) 1.3694; N(2)–C(1) 1.3975; N(2)–C(4) 1.3887; N(2)–C(15) 1.4368; C(15)–C(16) 1.3264.

trimethylsilyl group prevented the second hydroamination reaction completely (Figure 2). When aniline was reacted

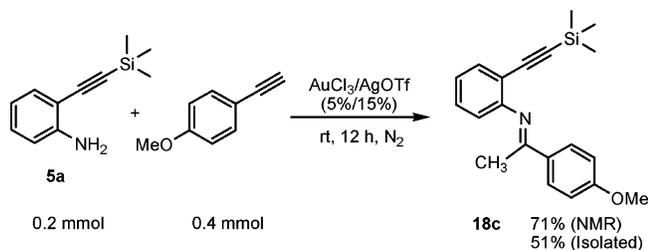


Figure 2. Gold(III)-catalyzed hydroamination of 2-[(trimethylsilyl)ethynyl]aniline with 1-ethynyl-4-methoxybenzene.

with arylacetylene, only phenylimine was obtained as the final product (Figure 3).

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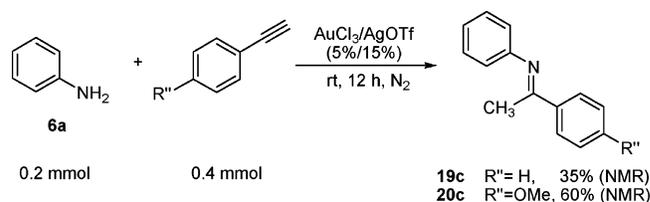


Figure 3. Gold(III)-catalyzed hydroamination of aniline with arylacetylene.

To understand the mechanism of the reaction, we examined two other reactions (Figure 4). The desired product (**1c**)

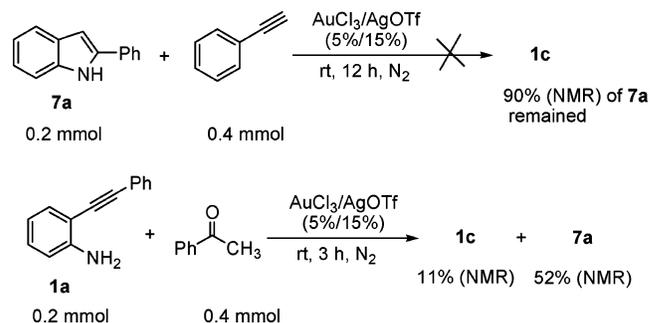


Figure 4. Gold(III)-catalyzed hydroamination.

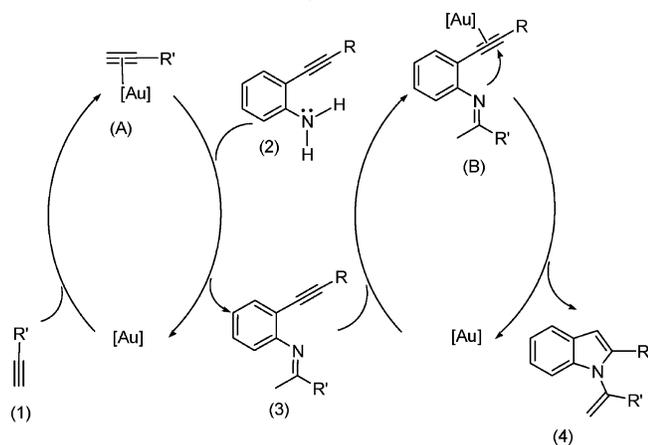
was not observed after 2-phenyl-1*H*-indole (**7a**) and phenylacetylene were stirred together at room temperature in the presence of AuCl₃/AgOTf for 12 h, and 90% of **7a** remained unreacted. However, the reaction of 2-(phenylethynyl)aniline with acetophenone gave compound **1c** in 11% NMR yield after being stirred at rt for 3 h. This result suggests that the first step of this reaction is the intermolecular hydroamination, which is followed by the intramolecular hydroamination.¹³

Therefore, a tentative mechanism for the gold (III)-catalyzed double hydroamination is proposed in Scheme 1. Terminal alkyne **1** is activated by Au(OTf)₃ to generate the intermediate **A**. **A** further reacts with **2** to yield the first hydroamination product **3**. Then the carbon–carbon triple bond of **3** is activated by Au(OTf)₃ again and produces the intermediate **B** via nucleophilic addition of the imine nitrogen. Finally, the C-3-position of indole is protonated to give the final product **4** and the catalyst is regenerated.

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Scheme 1. Tentative Mechanism for the Gold(III)-Catalyzed Double Hydroamination



In conclusion, a highly efficient double-hydroamination of *o*-alkynylanilines with terminal alkynes leading to *N*-vinylindoles was developed. This approach is simple, and double-hydroamination could be accomplished in a one-pot process, under mild conditions without solvent. The detailed mechanism and the scope of the reaction, especially the reason for the intermolecular hydroamination prior to the direct intramolecular indole formation, are currently under investigation.

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

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