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Gold(I)-Catalyzed Tandem Reactions Initiated by Hydroamination of Alkynyl Carbamates: Application to the Synthesis of Nitidine

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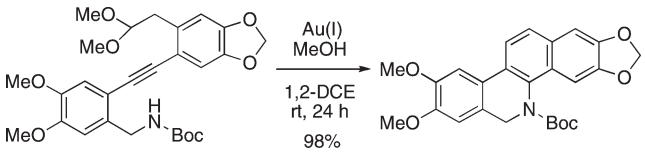

As a convenient and direct synthesis of 1,2-dihydroisoquinolines, the gold(I)-catalyzed intramolecular hydroamination of (2-alkynyl)benzyl carbamates has been developed. The reaction with cationic gold(I) complex [$AuCl(PPh_3)/AgNTf_2$] proceeded at room temperature, giving the desired 6-*endo* adducts. The addition of alcohol efficiently promoted the reaction, and the amount of the catalyst could be reduced to 1 mol %. However, the alkynes bearing either an electron-deficient aryl group or an alkyl group resulted in predominant production of 5-*exo* adducts. In such cases, use of a bulky gold catalyst, $AuCl[(o\text{-biPh})(^tBu)_2P]Cl/AgNTf_2$, improved the regioselectivity, giving the 6-*endo* adducts in better yields. Furthermore, the hydroamination of alkynyl carbamates bearing an acetal or enone was successfully applied to the concise synthesis of tetracyclic heterocycles such as nitidine via the single catalyst-mediated tandem cyclization which consists of a condensation or a Michael addition of the resulting enecarbamates.

Introduction

Both isoqinolines and hydroisoquinolines are found in many biologically active natural products and pharmaceutically relevant compounds, and they play a key role in their activities.[1] Their structural novelty and diverse biological activities stimulate many synthetic chemists to develop efficient synthetic methods for highly functionalized tetrahydroisoquinolines[2] as well as to discover a series of cascade reactions for diversity-oriented synthesis with an aim of construction of tetrahydroisoquinoline-based small molecular libraries.[3] Among the isoquinoline derivatives, we focused on benzo[*c*]phenanthridine alkaloids,[4] such as nitidine and fagaronine (Figure 1), because these compounds are considered as promising antitumor drug candidates due to their strong antitumor activity by the inhibition of DNA topoisomerase I.[5] Although a number of elegant synthesis of the 1,2-dihydroisoquinolines have been developed,[6] there are yet a few convenient methods for 3-substituted and 4-substituted 1,2-dihydroisoquinolines.[7]Recently, transition-metal-catalyzed 6-*endo*-mode cyclizations of 2-(1-alkynyl)-arylaldimines were discovered as a powerful synthetic tool

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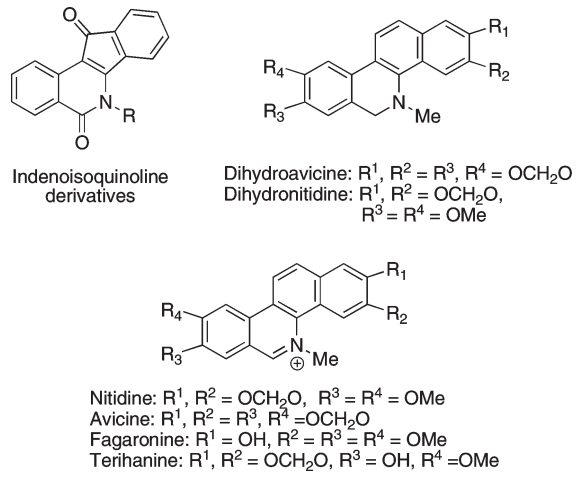

FIGURE 1. Structure of some benzo[*c*]phenanthridine alkaloids.

of such isoquinolines and 1,2-dihydroisoquinolines and also successfully applied to the total synthesis of natural products.[8] In contrast to these results, there are few reports on the synthesis of 3-substituted 1,2-dihydroisoquinolines through intramolecular hydroamination[9] of alkynylbenzylamine derivatives.[10]

On the other hand, the development of tandem reactions for the efficient construction of complex molecules is also an important goal of organic syrnthesis from the viewpoints of operational simplicity and assemble efficiency.[11] We envisaged that 1,2-dihydroisoquinoline scaffolds can be used as templates for the tandem reaction discovery. As outlined in Scheme 1, treatment of alkynyl carbamates **A** with a carbophilic Lewis acid[12] provides the desired dihydroisoquinoline **C** via cycloisomerization. If the resultant product **C**, bearing an enecarbamate moiety, possesses an another reactive site such as ketone, acetal, or electron-deficient double bond in the molecule, the subsequent cyclization of **C** would occur to give the polycyclic hydroisoquinoline alkaloids **F**. We have already reported the synthesis of several 1,2-dihydroisoquinolines through cycloisomerization and nucleophilic addition of 2-(alkynyl)phenylaldimines in the presence of an alkynophilic metal catalyst (Ni, In, or Au) and a proper nucleophile.[13] Furthermore, we recently described the gold-catalyzed intramolecular hydroamination of 2-(alkynyl)-benzyl carbamates as a general approach toward the synthesis of 2,3-disubstituted 1,2-dihydroisoquinolines.[14]

Herein, we describe the full detail of a scope and limitation of gold(I)-catalyzed cycloisomerization[15] of 2-(alkynyl)-benzyl carbamates together with an extension of the tandem reaction to alkynyl carbamates bearing appropriate functional groups for the synthesis of benzo[*c*]phenanthridine alkaloids.

Results and Discussion

Lewis Acid-Catalyzed Intramolecular Hydroamination of 2-Alkynylbenzyl Carbamates. We first investigated the intramolecular hydroamination of *N*-Boc-2-(phenylethynyl)-benzylamine **1a**[16] in the presence of several Lewis acid catalysts. The reaction of **1a** was carried out with 10 mol % of group 10 or 11 metal salts in 1,2-dichloroethane (1,2-DCE) (Table 1). First trials with $PdCl_2(PhCN)_2$, $Cu(OTf)_2$,

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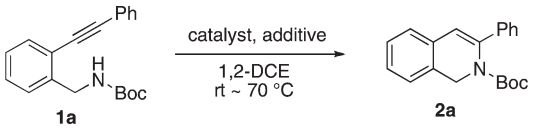
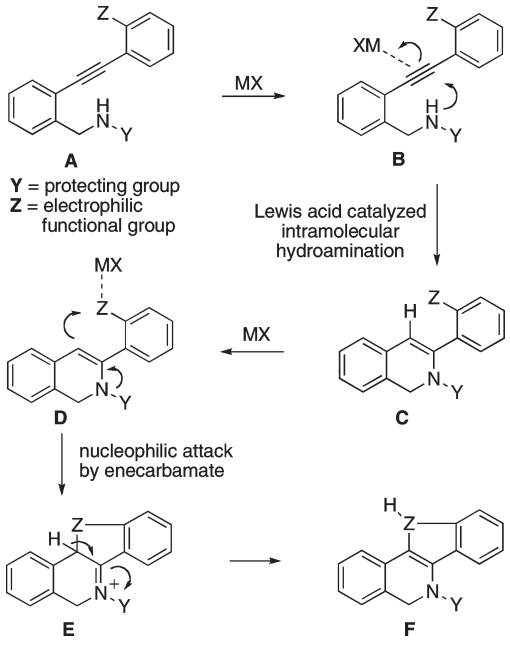
TABLE 1. Optimization of Catalysts for Hydroamination of 1a[a]



entry	catalyst	mol %	additive (5 equiv)	temp (°C)	time (h)	yield[b] (%) 2a	yield[b] (%) 1a
1	$AgNTf_2$	10		70	24	7	67
2	$PtCl_2$	10		70	24	46	
3	$Au(2\text{-}PyCO_2)Cl_2$	10		rt	24	30	50
4	$AuCl(PPh_3)$	10		70	24	N.R.	
5	$AuCl(PPh_3)/AgNTf_2$	10		rt	1	75	
6	$AuCl(PPh_3)/AgNTf_2$	1		rt	48	53	28
7	$AuCl(PPh_3)/AgNTf_2$	1	AcOH	rt	24	54	16
8	$AuCl(PPh_3)/AgNTf_2$	1	CF_3CH_2OH	rt	24	51	30
9	$AuCl(PPh_3)/AgNTf_2$	1	MeOH	rt	2	81	
10	$AuCl(PPh_3)/AgNTf_2$	1	EtOH	rt	2	83	
11	$AuCl(PPh_3)/AgNTf_2$	1	^{i}PrOH	rt	4	77	
12	$AuCl(PPh_3)/AgNTf_2$	1	^{t}BuOH	rt	9	79	

[a]Reactions were carried out with *N*-Boc-benzylamine **1a** and additive (5 equiv) in the presence of several Lewis acids (1−10 mol %) at rt to 70 °C. [b]Isolated yield.

SCHEME 1. Lewis Acid Catalyzed Tandem Cyclization of A



and $AgNTf_2$ did not give any good results, providing the desired product **2a** in up to 7% yield (entry 1). When $PtCl_2$[15c,17] or $Au(2\text{-}PyCO_2)Cl_2$[18] was used as the catalyst, **2a** was obtained in moderate yield (entries 2 and 3). Although $AuCl(PPh_3)$ itself did not catalyze the cyclization of **1a** at all, a cationic gold(I) complex, generated from $AuCl(PPh_3)$ and $AgNTf_2$,[19] efficiently promoted the reaction even at room temperature to give **2a** in 75% yield (entries 4 and 5). Encouraged by this result, we next examined the amount of the catalyst in the presence of several additives. The amount of the cationic gold complex was reduced to 1 mol %, resulting in incomplete consumption of **1a** (entry 6). Unexpectedly, the addition of 5 equiv of EtOH or MeOH to the reaction mixture dramatically accelerated the Au(I)-catalyzed cyclization to give the desired product **2a** in good yield within 2 h. However, such effect became weaker in the cases of ^{i}PrOH and ^{t}BuOH. Furthermore, AcOH or CF_3CH_2OH had no effect on the reaction rate (entries 7−12). Relatively stronger protic acids such as CF_3SO_3H or AcOH are known to accelerate gold-catalyzed hydroamination as well as other gold-catalyzed reactions.[20] In contrast to these results, less acidic and less bulky alcohols showed a striking effect in this reaction.

Having established the optimized reaction conditions, we applied this method to a variety of substrates **1b**−**m** bearing different R^1 and R^2 substituents for the synthesis of various 1,2-dihydroisoquinolines (Table 2). All reactions were carried out in 1,2-DCE at room temperature in the presence of the cationic gold catalyst (1 mol %) and EtOH (5 equiv). As a result, not only Boc but also Cbz, *p*-methoxyphenyl (PMP), and Ms groups can be used as a protecting group (R^1) of the benzylamine derivatives **1b**−**d**, giving the corresponding cyclized adducts **2b**−**d** in 81−83% yields (entries 1−3). In addition, the substituent (R^2) of the alkynyl group significantly affected on the chemical yield of **2** and the 6-*endo*/5-*exo* selectivity by changing electron density on the triple bond (entries 4−12). The substrates **1e**−**h** bearing an aryl group with the electron-donating groups such as methyl, hydroxymethyl, methoxy, and chloride generally furnished the desired 6-*endo* adducts in good yields, while 5 mol % of the catalyst was required to complete the reaction of

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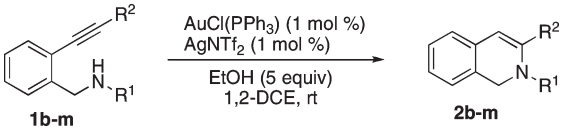
TABLE 2. Au(I)-Catalyzed Hydroamination of 2-Alkynylbenzylamines 1b−m



entry	substrate	R^1	R^2	time (h)	product	yield[a] (%)
1	**1b**	Cbz	Ph	4	**2b**	83
2	**1c**	PMP	Ph	0.5	**2c**	82
3	**1d**	Ms	Ph	7	**2d**	81
4	**1e**	Boc	3,5-$Me_2C_6H_3$	2	**2e**	87
5	**1f**	Boc	4-ClC_6H_4	2	**2f**	71
6	**1g**	Boc	4-$HOCH_2C_6H_4$	3	**2g**	79
7[b]	**1h**	Boc	4-$MeOC_6H_4$	2	**2h**	87
8	**1i**	Boc	4-NCC_6H_4	24	**2i**	N.R.
9	**1j**	Boc	^{t}Bu	24	**2j**	N.R.
10	**1k**	Boc	H	2	**2k**	0
11	**1l**	Boc	^{n}Pr	6	**2l**	28
12	**1m**	Boc	4-$MeOCOC_6H_4$	24	**2m**	20 (15)[c]
13[d]	**1l**	Boc	^{n}Pr	0.2	**2l**	98
14[d]	**1a**	Boc	Ph	0.5	**2a**	91
15[d]	**1m**	Boc	4-$MeOCOC_6H_4$	24	**2m**	37 (6)[c]
16[d,e]	**1j**	Boc	^{t}Bu	48	**2j**	32 (61)[c]

[a]Isolated yield. [b]5 mol % of the Au(I) catalyst was used. [c]Values in parentheses are yields of recovered starting materials. [d]Reactions were carried out without EtOH, and AuCl[(*o*-biPh)(^{t}Bu)$_2$P] (1 mol %) was used instead of $AuCl(PPh_3)$. [e]The reaction was heated at 50 °C.

carbamate **1h** which has a 4-OMe substituent. In contrast, the current reaction revealed to be not effective for the 6-*endo* cyclization of the substrates **1i**−**m** bearing either an electron-deficient aryl group or an alkyl group. Indeed, the reaction of **1i** and**1j** did not take place at all and only recovered the starting material, but the same treatment of **1k** resulted in a complex mixture of products. Moreover, subjection of alkyne **1l** and ester **1m** to the same reaction conditions afforded the dihydroisoquinolines **2l** and **2m** in 28 and 20% yields, respectively, together with a mixture of unidentified compounds. To improve the regioselectivity, a bulkier gold(I) catalyst was examined (entries 13−15). The reaction of **1l** with AuCl[(*o*-biPh)(^{t}Bu)$_2$P]/$AgNTf_2$[15i,21] (1 mol %) not only enhanced the reaction rate but also increased the chemical yield to 98%. Interestingly, the same treatment of **1a** and **1m** led to somewhat different results. Although **1a** provided the desired product **2a** in better yield (91%) (entry 10 in Table 1), the 6-*endo* adduct **2m** was obtained in only 37% yield. Even with the bulky gold(I) catalyst, the 6-*endo* cyclization of electron-deficient arylalkynes took place sluggishly.

We presumed these unidentified compounds might be the corresponding 5-*exo* adducts, but unfortunately, we could not isolate these products. We then undertook the intermolecular trapping experiment of the presumed 5-*exo* adducts with *N*-methylmaleimide in order to identify these side products[10b] (Scheme 2). For this purpose, pentynyl carbamate **1l** was selected as a suitable substrate for the 5-*exo* cyclization. In fact, the reaction of **1l** with the gold catalyst (1 mol %) afforded the 6-*endo* adduct **2l** in only 28% yield (Table 2, entry 11). However, when the same reaction was

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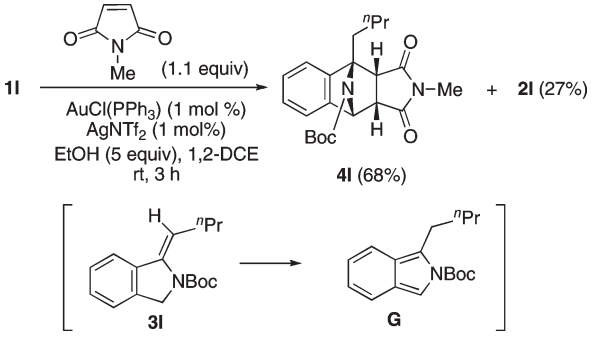
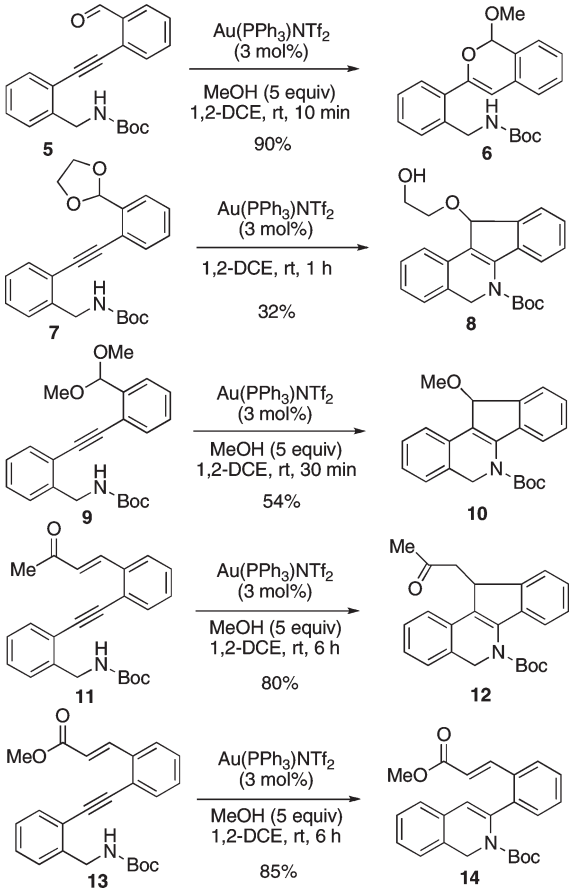
SCHEME 2. Intermolecular Trapping of 5-*exo* Adducts

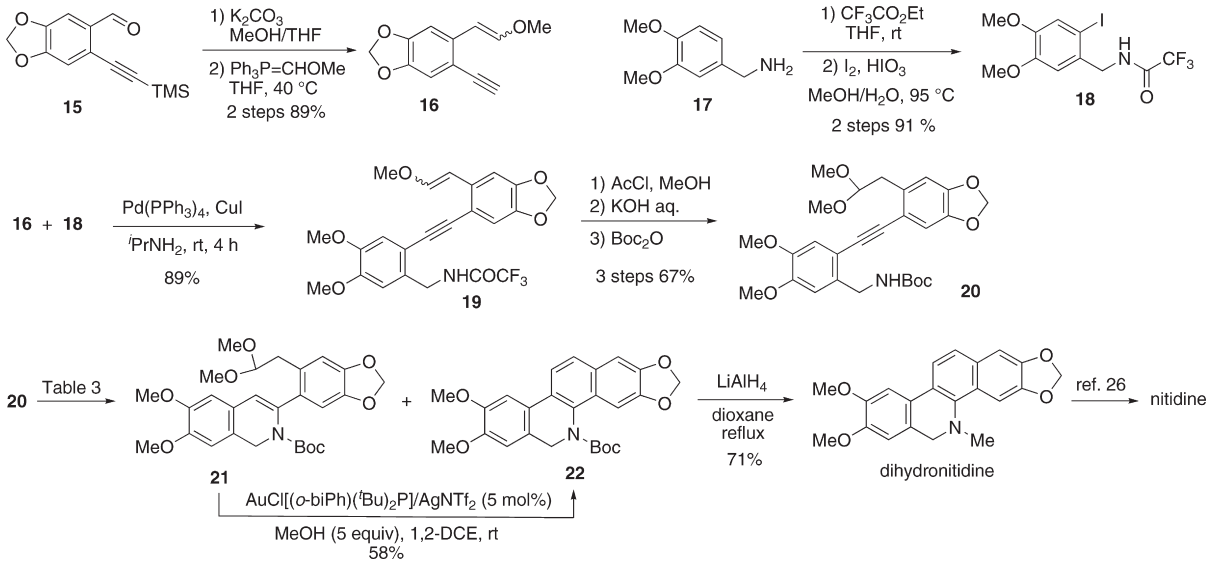


SCHEME 3. Gold(I)-Catalyzed Tandem Cyclization



carried out with 1.1 equiv of *N*-methylmaleimide, new product **4l** was obtained in 68% yield along with 27% yield of **2l**. The relative configuration of **4l** shown in Scheme 2 was determined by the NOESY experiment. The Diels−Alder adduct **4l** was probably formed via the 5-*exo* cyclization of **1l**, subsequent isomerization of 5-*exo* adduct **3l** to labile isoindole intermediate **G**, and Diels−Alder type cycloaddition with maleimide. On the basis of these results, the low yields of dihydroisoquinolines **2k**−**m** is obviously attributed to the predominant occurrence of the 5-*exo* cyclization of **1k**−**m**. We proved that the substitution of the R^2 group to either an alkyl or an electron-deficient aryl group promoted the 5-*exo* cyclization to give the corresponding isoindole derivatives which could not be isolated due to their instability.

SCHEME 4. Total Synthesis of Nitidine



The Au(I)-Mediated Tandem Reaction of Alkynyl Carbamates Bearing Several Electrophiles. In order to apply the intramolecular hydroamination into tandem reaction[8c,d,15t,u,x,22] for the synthesis of polycyclic compounds, we planned to utilize high nucleophilic activity of enecarbamates,[23] which can be easily synthesized by the Au(I)-catalyzed intramolecular hydroamination with various electrophiles (Scheme 3). We initially examined the tandem reaction of aldehyde **5**, because the gold catalyst would be expected to activate both C−C triple bond and formyl group. However, instead of the carbamate, aldehyde exclusively attacked the triple bond in a 6-*endo* mode to give bicyclic acetal **6** as the single product.[24] To suppress the nucleophilic addition by the formyl group, cyclic acetal **7** and dimethyl acetal **9** were prepared and their reactivity was examined. When we carried out the reaction with acetal **7** in the presence of methanol, a complex mixture was obtained due to the acetal-exchange reaction. Therefore, in the case of **7**, methanol was not added to the reaction mixture. Consequently, both compounds **7** and **9** underwent the tandem reaction of the 6-*endo* hydroamination and aldol condensation to give the desired tetracyclic adducts **8** and **10** with 32% and 54% yields, respectively. Under these conditions, the corresponding hydroamination adducts were not observed as a reaction intermediate, probably because the second cyclization with the acetal might be much faster than the first hydroamination. Furthermore, it was revealed that α,β-unsaturated ketone could be used as an electrophile for the second cyclization.[22] Indeed, the enone **11** underwent the tandem cyclization efficiently to give the ketone **12** in 80% yield. However, during this reaction, a dihydroisoquinoline intermediate was observed on TLC due to slower reaction rate of the subsequent Michael addition than that of the first step. Then, the reaction required a long reaction time (6 h) to complete the tandem cyclization. In contrast, the tandem reaction of enoate **13** did not occur due to the insufficient electrophilicity of the enoate as a Michael acceptor, providing the corresponding hydroisoquinoline **14** in 85% yield.

Application of the Tandem Reaction to Formal Total Synthesis of Nitidine. Since the gold(I)-catalyzed hydroamination of alkynylbenzyl carbamate **9** bearing the acetal moiety efficiently provided the tetracyclic compound **10**, our attention was next directed toward the total synthesis of polycyclic natural products such as nitidine by using this tandem reaction. The requisite *N*-Boc-alkynylbenzylamine **20** for the tandem reaction was prepared from aldehyde **15**[25] and benzylamine derivative **17** (Scheme 4). Successive treatment of **15** with K_2CO_3 in methanol and Wittig reagent (Ph_3P=CHOMe) provided the desired arylethyne **16** in 89% yield. The aryl iodide **18** was synthesized from **17** in good yield by trifluoroacetylation with CF_3CO_2Et and the subsequent iodination with I_2 and HIO_3. The Pd-catalyzed Sonogashira reaction of **16** and **18** proceeded smoothly, and the requisite acetal **20** was synthesized by the acetalization, hydrolysis, and *N*-Boc protection of the resulting acetamide **19** without any troubles. We next investigated the tandem cyclization under the optimized conditions

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SCHEME 5. Reaction Mechanism of the Au(I)-Catalyzed Tandem Cyclization

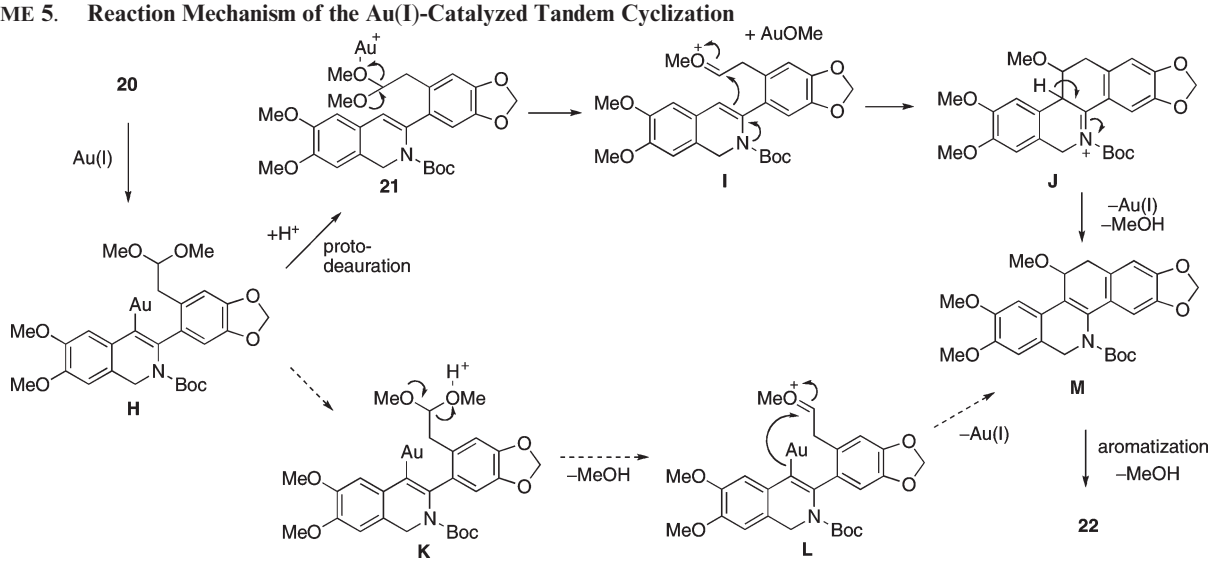

TABLE 3. Au(I)-Catalyzed Tandem Cyclization of 20

				yield[b] (%)	
entry	catalyst[a]	Au(I) (mol %)	MeOH (equiv)	**21**	**22**
1	A	3	5	20	74
2	A	3	0	53	19
3	A	5	5	10	88
4	B	5	0	50	47
5	B	5	5	trace	98

[a]Key: (A) $AuCl(PPh_3)/AgNTf_2$, rt, 24 h; (B) AuCl[(*o*-biPh)(^{t}Bu)$_2$P]/$AgNTf_2$, rt, 24 h. [b]Isolated yield.

(Table 3). In contrast to the one-carbon homologue **9**, the tandem reaction of **20** proceeded slowly even with 3 mol % of the gold complex $AuCl(PPh_3)/AgNTf_2$ to afford dihydroisoquinoline **21** and the desired policyclic product **22** in 20% and 74% yields, respectively (entry 1). No addition of methanol to the reaction resulted in deceleration of both the hydroamination and condensation, and further increasing the catalytic amount of the catalyst did not improve the chemical yields dramatically (entries 2 and 3). After screening various catalysts, sufficient improvement was achieved by using the bulkier gold(I) catalyst, AuCl[(*o*-biPh)(^{t}Bu)$_2$P]Cl/$AgNTf_2$. In this case, the addition of methanol promoted the second condensation reaction to give the desired product **22** in 98% yield (entries 4 and 5).

The reaction mechanism of the tandem cyclization of **20** is shown in Scheme 5. Since the dihydroisoquinoline **21** was always observed on TLC during the reaction, **21** would be a reaction intermediate, which was obtained regioselectively by the Au(I)-catalyzed intramolecular hydroamination of **20** via **H**. The subsequent activation of the acetal moiety of **21** by the same Au(I)-catalyst promoted the intramolecular Mukaiyama-type aldol condensation with the enecarbamate moiety via **I** to **J** to afford labile 5,6,11,12-tetrahydrobenzo[*c*]phenanthridine **M**. Since subjection of the isolated **21** to the cyclization conditions of **20** provided the same product **22** in 58% yield along with the starting material **21** (33%), another mechanism in which the alkenylgold moiety of **H** directly acts as a nucleophile for the Mukaiyama-type aldol condensation via **K** to **L** cannot be excluded to provide **M**. In any event, the oxidative aromatization of the resulting unstable compound **M** would take place to give the corresponding 5,6-dihydrobenzo[*c*]phenanthridine **22** in good yield. Finally, the reduction of **22** with $LiAlH_4$ furnished dihydronitidine as the single product, which was identical to the reported compound by comparing their spectral data with an authentic sample.[26] Since dihydronitidine had been already converted into nitidine by two steps, we achieved a formal total synthesis of nitidine.

Conclusion

We have demonstrated that the nitrogen atom of (2-alkynyl)benzylamines acts as a reactive nucleophile in the Au(I)-catalyzed hydroamination, irrespective of the substituents on the nitrogen atom. The Au(I) catalysts such as $AuCl(PPh_3)/AgNTf_2$ or AuCl[(*o*-biPh)(^{t}Bu)$_2$P]Cl/$AgNTf_2$ are efficient carbophilic Lewis acids for the 6-*endo* cyclization. Furthermore, the resulting *N*-Boc-1,2-dihydroisoquinolines were revealed to be versatile synthetic intermediates for the further C−C bond formation at C4 position. The tandem cyclization of alkynyl carbamates bearing an acetal or enone was successfully applied to the concise synthesis of tetracyclic heterocycles such as dihydronitidine via the single catalyst-mediated tandem reaction which consists of a condensation or a Michael addition of the resulting enecarbamates.

Experimental Section

Typical Procedure for the Gold(I)-Catalyzed 6-*Endo* Hydroamination. To a solution of alkynyl carbamate **1a** (309 mg, 1.00 mmol) in 1,2-dichloroethane (2.0 mL) was added a mixture of $AuCl(PPh_3)$ (4.9 mg, 0.0099 mmol), $AgNTf_2$ (3.8 mg, 0.0098 mmol), EtOH (293 μL, 5.02 mmol), and 1,2-dichloroethane (1.0 mL) at room temperature. After the mixture was stirred for 2 h, a saturated aqueous $NaHCO_3$ solution was added, and the resulting mixture was extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by

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silica gel column chromatography (hexane/AcOEt = 25/1) to afford **2a** (256 mg, 83%) as colorless crystals.

***tert*-Butyl 3-Phenylisoquinoline-2(1*H*)-carboxylate (2a).** Mp: 105−106 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, 2H, J = 7.3 Hz), 7.36 (dd, 2H, J = 7.3, 7.1 Hz), 7.30 (t, 1H, J = 7.1 Hz), 7.27−7.18 (m, 4H), 6.42 (s, 1H), 4.89 (s, 2H), 1.05 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.0, 140.6, 139.0, 132.7, 132.0, 128.1, 127.7, 127.5, 127.2, 126.3, 125.1, 125.0, 115.2, 81.0, 47.5, 27.6. IR ($CHCl_3$) ν 3011, 1693 cm^{-1}. MS (FAB$^+$): m/z 307 [M]$^+$ (100), 251 (96), 206 (53). Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.23; H, 7.07; N, 4.48.

Synthesis of 22 by the Gold(I)-Catalyzed Tandem Cyclization (Table 3, Entry 5). To a solution of alkynyl carbamate **20** (69.8 mg, 0.140 mmol) in 1,2-dichloroethane (0.2 mL) was added a mixture of AuCl[(*o*-biPh)(^{t}Bu)$_2$P] (3.7 mg, 0.0070 mmol), $AgNTf_2$ (2.7 mg, 0.0070 mmol), MeOH (28 μL, 0.70 mmol), and 1,2-dichloroethane (0.27 mL) at room temperature. After being stirred for 24 h, saturated aqueous $NaHCO_3$ was added, and the resultant mixture was extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 4/1) to afford **22** (59.9 mg, 98%) as a white powder.

***tert*-Butyl 2,3-Dimethoxy[1,3]benzodioxolo[5,6-*c*]phenanthridine-12(13*H*)-carboxylate (22).** Mp: 183−184 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, 1H, J = 8.6 Hz), 7.57 (d, 1H, J = 8.6 Hz), 7.34 (s, 1H), 7.25 (s, 1H), 7.09 (s, 1H), 6.84 (s, 1H), 6.03 (br s, 2H), 5.31 (br s, 1H), 4.14 (d, 1H, J = 15.1 Hz), 3.98 (s, 3H), 3.94 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.1, 148.68, 148.66, 147.8, 147.3, 133.0, 130.2, 128.0, 126.7, 125.5, 125.3, 119.8, 108.9, 107.1, 103.8, 101.7, 101.1, 81.0, 56.1, 56.0, 47.4, 28.1 (one carbon peak was missing due to overlapping). IR (ATR) ν 2935, 2859, 1716 cm^{-1}. MS (FAB$^+$): m/z 435 [M]$^+$ (38), 379 (75), 334 (100). HRMS (FAB$^+$): calcd for $C_{25}H_{25}NO_6$ [M]$^+$ 435.1682, found 435.1685.

Experimental Procedure for the Intermolecular Trapping of 5-*Exo* Adduct. To a solution of alkynyl carbamate **1l** (274 mg, 1.00 mmol) and *N*-methylmaleimide (123 mg, 1.11 mmol) in 1,2-dichloroethane (2.0 mL) was added a mixture of AuCl(PPh$_3$) (5.0 mg, 0.010 mmol), $AgNTf_2$ (4.0 mg, 0.010 mmol), EtOH (292 μL, 5.00 mmol), and 1,2-dichloroethane (1.0 mL) at room temperature. After the mixture was stirred for 3 h, a saturated aqueous $NaHCO_3$ solution was added, and the resultant mixture was extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 25/1 to 4/1) to afford **2l** (74 mg, 27%) as a pale yellow oil and **4l** (262 mg, 68%) as a colorless oil.

***tert*-Butyl (3a*R**,4*S**,9*R**,9a*S**)-4-Butyl-2-methyl-1,3-dioxo-2,3,3a,4,9,9a-hexahydro-1*H*-4,9-epiminobenzo[*f*]isoindole-10-carboxylate (4l).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26−7.18 (m, 3H), 7.11 (d, 1H, J = 6.5 Hz), 5.48 (d, 1H, J = 5.4 Hz), 3.74 (dd, 1H, J = 8.1, 5.4 Hz), 3.41 (d, 1H, J = 8.1 Hz), 2.76−2.69 (m, 1H), 2.67−2.60 (m, 1H), 2.23 (s, 3H), 1.65−1.57 (m, 2H), 1.54−1.45 (m, 2H), 1.47 (s, 9H), 0.97 (t, 3H, J = 7.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.7, 174.6, 154.3, 141.7, 138.5, 127.7, 127.6, 121.4, 120.6, 81.4, 75.5, 63.3, 51.7, 49.1, 29.1, 28.2, 26.9, 23.8, 23.1, 14.1. IR (ATR) ν 3022, 2960, 2872, 1779, 1703, 1699 cm^{-1}. MS (FAB$^+$): m/z 385 [M + H]$^+$ (22), 329 (100), 285 (73), 268 (45). HRMS (FAB$^+$): calcd for $C_{22}H_{28}N_2O_4$ [M]$^+$ 384.2049, found 384.2047.

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Supporting Information Available: Experimental procedure and characterization data for all obtained compounds and ^{1}H and ^{13}C NMR spectra of all obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.