Gold(I)-Catalyzed Hydroamination as a General Approach toward the Synthesis of Substituted Hydroisoquinolines: Remarkable Acceleration by Ethanol

Taro Enomoto, Shingo Obika, Yoshizumi Yasui, Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan
Fax +81(75)7534569; E-mail: takemoto@pharm.kyoto-u.ac.jp

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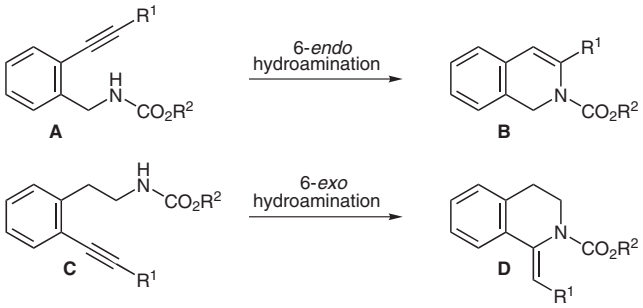
Abstract: Construction of 1,2-dihydroisoquinolines and 1-alkylidenyl-1,2,3,4-tetrahydroisoquinolines through cationic gold(I) complex catalyzed hydroamination of the corresponding alkynyl carbamates has been demonstrated. In the presence of EtOH, the reaction proceeded smoothly at room temperature with low catalyst loading (1–3 mol%).

Key words: hydroamination, isoquinolines, catalysis, heterocycles, cyclizations

Synthesis of substituted hydroisoquinolines has received continuous attention because of their frequent occurrence as key structural subunits in numerous biologically and medicinally important molecules.[1] Recently, we reported a synthesis of 1,2-dihydroisoquinolines through addition–cyclization of 2-(alkynyl)phenylaldimines in the presence of an alkynophilic metal catalyst (Ni, In, or Au) and a nucleophile.[2,3] We became interested in expanding such alkynophilic catalyst-mediated cyclization toward the synthesis of different types of hydroisoquinolines. Scheme 1 describes our approach which utilizes intramolecular hydroamination of alkynyl carbamates in two modes. Starting from 2′-alkynylbenzylcarbamate **A**, if 6-*endo* hydroamination occurs, 1,2-dihydroisoquinoline **B** should be obtained.[4] On the other hand, when the one-carbon homologue, 2′-alkynylphenetylcarbamate **C**, is cyclized in a 6-*exo* mode, 1-alkylidenyl-1,2,3,4-tetrahydroisoquinoline **D** will be formed.[5] These reactions are isomerization processes that possess high atom economy. Moreover, if carbamates could act as a nucleophilic domain, the product will be enecarbamates, which are attractive synthetic intermediates due to their rich synthetic transformations.[6] In contrast to relatively nucleophilic amines, hydroamination of alkynyl amides and carbamates to form six-membered rings under mild conditions is a challenging task.[7]

Transition-metal-catalyzed hydroamination of alkynyl amine derivatives has been studied widely to access a variety of nitrogen-containing molecules.[8] However, there are only a few examples of hydroisoquinoline formations.[9] Usually in these examples, substituents on the amino group are limited to alkyl or aryl groups, and high catalyst loading at elevated temperature is necessary.



Scheme 1 Hydroisoquinoline synthesis through intramolecular hydroamination

To investigate the 6-*endo* intramolecular hydroamination, *N*-Boc-2-(phenylethynyl)phenylmethylamine (**1a**) was treated with group 10 or 11 metal salts in 1,2-dichloroethane (DCE) (Table 1). First attempt was carried out in the presence of 10 mol% of $PdCl_2(PhCN)_2$ at 70 °C for 24 hours (entry 1). After aqueous workup and silica gel chromatography, the desired 1,2-dihydroisoquinoline **2a** was isolated in 5% yield with 63% of unreacted **1a**.[10,11] When $PtCl_2$ was used, starting material was consumed in 24 hours and **2a** was obtained in 46% yield (entry 2). CuI or $Cu(OTf)_2$ was totally ineffective (entries 3 and 4). $AgNTf_2$ gave a similar result in the case of $PdCl_2(PhCN)_2$ (entry 5). Although $AuCl(PPh_3)$ itself did not promote the cyclization (entry 6), a cationic gold(I) complex, generated from $AuCl(PPh_3)$ and $AgNTf_2$,[12] catalyzed the reaction efficiently.[13,14] Upon stirring for one hour at room temperature, **2a** was isolated in 75% yield (entry 7). Encouraged by this result, the amount of catalyst was reduced to 1 mol%, but **1a** was not transformed completely to **2a** even after 48 hours (entry 8). To accelerate the reaction, addition of protic additives was examined. Though AcOH and CF_3CH_2OH had less effect (entries 9 and 10), by adding five equivalents of EtOH, the reaction reached completion in two hours at room temperature to give **2a** in 83% isolated yield (entry 11). Relatively stronger protic acids such as CF_3SO_3H or AcOH are known to accelerate gold-catalyzed hydroaminations[15] as well as other gold-catalyzed reactions.[16] In contrast to these reports, less acidic EtOH showed striking effect in our case.

Having the optimized conditions in hand, we carried out the synthesis of a variety of 1,2-dihydroisoquinolines (Table 2). Not only Boc but also Cbz, Ms or 4-methoxyphenyl (PMP) groups can be used as a substituent on the

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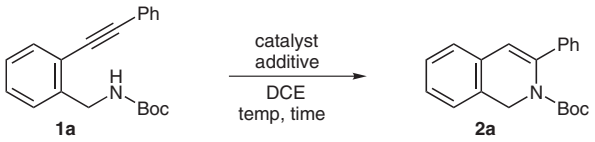
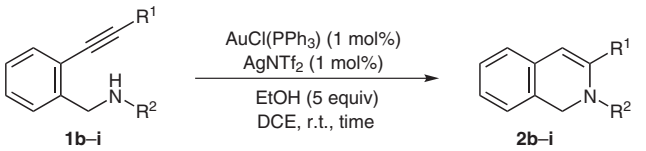
Table 1 Hydroamination of *N*-Boc-*o*-alkynylbenzylamine **1a**

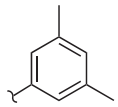
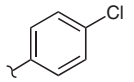
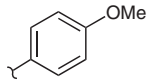
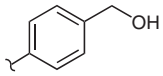


Entry	Catalyst (mol%)	Additive (5 equiv)	Temp (°C)	Time (h)	Yield (%)[a]
1	$PdCl_2(PhCN)_2$ (10)		70	24	5 (63)
2	$PtCl_2$ (10)		70	24	46
3	CuI (10)		70	24	0[b]
4	$Cu(OTf)_2$ (10)		70	24	0[b]
5	$AgNTf_2$ (10)		70	24	7 (67)
6	$AuCl(PPh_3)$ (10)		70	24	0[b]
7	$AuCl(PPh_3)$ (10) $AgNTf_2$ (10)		r.t.	1	75
8	$AuCl(PPh_3)$ (1) $AgNTf_2$ (1)		r.t.	48	53 (28)
9	$AuCl(PPh_3)$ (1) $AgNTf_2$ (1)	AcOH	r.t.	24	54 (16)
10	$AuCl(PPh_3)$ (1) $AgNTf_2$ (1)	CF_3CH_2OH	r.t.	24	51 (30)
11	$AuCl(PPh_3)$ (1) $AgNTf_2$ (1)	EtOH	r.t.	2	83

[a] The yield in parentheses shows the recovered yield of compound **1a**.
[b] Only **1a** was detected.

Table 2 Synthesis of 1,2-Dihydroisoquinolines through Hydroamination



Entry	Substrate	R^1	R^2	Time (h)	Product	Yield (%)
1	**1b**	Ph	Cbz	4	**2b**	83
2	**1c**	Ph	Ms	7	**2c**	81
3	**1d**	Ph	PMP	0.5	**2d**	82
4	**1e**		Boc	2	**2e**	87
5	**1f**		Boc	2	**2f**	71
6[a]	**1g**		Boc	2	**2g**	87
7[b]	**1h**		Boc	3	**2h**	79
8	**1i**	Pr	Boc	6	**2i**	28

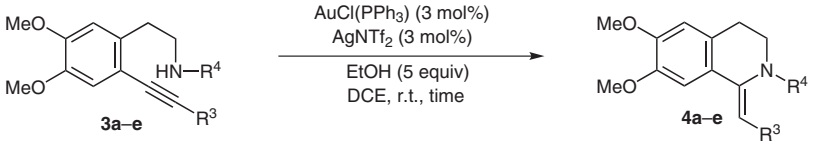
[a] $AuCl(PPh_3)$ (5 mol%) and $AgNTf_2$ (5 mol%) were used.
[b] Reaction was carried out in CH_2Cl_2 due to the low solubility of **1h** in DCE.

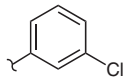
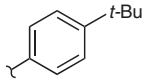
nitrogen (entries 1–3). The reaction rate increased in the following order: PMP > Boc > Cbz > Ms, which can be explained by the difference of nucleophilicity with respect to the nitrogen atom. Influence of the electron density on the alkynyl moiety was also observed. Though the cyclization of 3,5-dimethyl- or 4-chloro-substituted carbamates **1e** and **1f** finished in two hours under the standard conditions (entries 4 and 5), 5 mol% of the catalyst was required to complete the reaction of carbamate **1g** which has a 4-OMe substituent (entry 6). Alcohol **1h** was converted into dihydroisoquinoline **2h** in good yield (entry 7). Unfortunately, the current reaction conditions were not efficient for the 6-*endo* cyclization of alkyl acetylene derivatives; the reaction of 2-(1-pentynyl)phenylmethylamine **1i** gave only 28% of the desired isoquinoline **2i** together with a mixture of unidentified compounds (entry 8).[10]

The combination of $AuCl(PPh_3)$ and $AgNTf_2$ in the presence of EtOH was also effective for the 6-*exo* intramolecular hydroamination (Table 3). When *N*-Boc-phenethylamine **3a** was treated with 1 mol% of $AuCl(PPh_3)$ and $AgNTf_2$, the desired tetrahydroisoquinoline **4a** was obtained in 58% yield after stirring at room temperature for 48 hours (entry 1). Stereochemistry of the double bond was determined to be *Z* by NOE experiment, and supported by the high-field shift of the *N*-Boc signal in ^1H NMR spectra.[17] The reaction was highly stereoselective as no formation of the *E*-isomer was detected. This high stereoselectivity is remarkable since stereoselective synthesis of 1-alkylidenyl-1,2,3,4-tetrahydroisoquinolines is often troublesome.[18] By increasing the amount of the catalyst to 3 mol%, the reaction completed in five hours to give 87% isolated yield (entry 2). As in the 6-*endo* cyclization, substituents on the nitrogen atom influenced the reactivity. The cyclization of *N*-methoxycarbonyl derivative **3b** required 15 hours for completion (entry 3). Chlorophenyl derivative **3c** and *tert*-butylphenyl derivative **3d** cyclized without any difficulty (entries 4 and 5). The 1-pentynyl derivative **3e** also underwent the 6-*exo* cyclization to give 75% of butylidenyl tetrahydroisoquinoline **4e** (entry 6).

In conclusion, syntheses of substituted hydroisoquinolines through 6-*endo* and 6-*exo* hydroaminations have been developed.[19] The combination of the cationic gold(I) complex and EtOH was shown to promote the reaction efficiently at room temperature. From a scientific point of view, remarkable acceleration by EtOH is of great interest. The current method has promising advantage toward practical uses because of the mild reaction conditions, low catalyst loading, high chemoselectivity and high atom economy.

Table 3 Synthesis of 1-Alkylydenyl-1,2,3,4-tetrahydroisoquinoline through Hydroamination



Entry	Substrate	R^3	R^4	Time (h)	Product	Yield (%)[a]
1[b]	**3a**	Ph	Boc	48	**4a**	58 (6)
2	**3a**	Ph	Boc	5	**4a**	87
3	**3b**	Ph	CO_2Me	15	**4b**	78
4	**3c**		Boc	5	**4c**	76
5	**3d**		Boc	6	**4d**	86
6	**3e**	Pr	Boc	11	**4e**	75

[a] The yield in parentheses shows the recovered yield of compound **1a**.
[b] $AuCl(PPh_3)$ (1 mol%) and $AgNTf_2$ (1 mol%) were used.

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(10) The corresponding 5-*exo* cyclized products, namely isoindoles, were not detected in this work, presumably due to their instability.
(11) Structure of **2a** was fully confirmed by spectroscopy and by its conversion into known 3-phenylisoquinoline; from **1a**, 3-phenylisoquinoline was obtained in 70% yield after cleavage of Boc group (TFA, CH_2Cl_2, r.t., 30 min) followed by oxidation (I_2, KOAc, EtOH, reflux, 1 h).
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(19) **Typical Procedure for the Gold(I)-Catalyzed Hydroamination**: To a solution of **1a** (309 mg, 1.00 mmol) in DCE (2 mL) were added EtOH (231 mg, 293 μL, 5.02 mmol) and a suspension of $AuCl(PPh_3)$ (4.9 mg, 0.0099 mmol) and $AgNTf_2$ (3.8 mg, 0.0098 mmol) in DCE (1 mL) at r.t. After stirring for 2 h, sat. aq $NaHCO_3$ was added and the product was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 25:1) to afford **2a** (256 mg, 83%) as colorless crystals: R_f 0.70 (hexane–EtOAc, 3:1); mp 105–106 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.48 (d, *J* = 7.3 Hz, 2 H), 7.36 (dd, J_1 = 7.1 Hz, J_2 = 7.3 Hz, 2 H), 7.30 (t, *J* = 7.1 Hz, 1 H), 7.18–7.27 (m, 4 H), 6.42 (s, 1 H), 4.89 (s, 2 H), 1.05 (s, 9 H). ^{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 ($CHCl_3$): 1693 cm^{-1}. MS (FAB): *m*/*z* = 307 [M$^+$]. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; 4.56. Found: C, 78.23; H, 7.07; N, 4.48.

Compound **2e**: colorless crystals; R_f 0.55 (hexane–EtOAc, 6:1); mp 168–169 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.16–7.26 (m, 4 H), 7.09 (s, 2 H), 6.94 (s, 1 H), 6.41 (s, 1 H), 4.87 (s, 2 H), 2.33 (s, 6 H), 1.06 (s, 9 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.0, 140.8, 138.7, 137.5, 132.7, 131.9, 129.3, 127.5, 127.0, 125.0, 124.9, 124.1, 114.6, 80.8, 47.5, 27.6, 21.2. IR ($CHCl_3$): 1691 cm^{-1}. MS (FAB): *m*/*z* = 335 [M$^+$]. Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.66; H, 7.50; N, 4.23.

Compound **2h**: white powder; R_f 0.50 (hexane–EtOAc, 1:1); mp 115–116 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.46 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 7.15–7.26 (m, 4 H), 6.42 (s, 1 H), 4.85 (s, 2 H), 4.68 (s, 2 H), 2.58 (s, 1 H), 1.06 (s, 9 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.9, 140.6, 140.2, 137.9, 132.5, 131.8, 127.5, 127.2, 126.6, 126.2, 125.0, 124.9, 115.2, 81.0, 64.7, 47.4, 27.6. IR ($CHCl_3$): 3606, 1693 cm^{-1}. MS (FAB): *m*/*z* = 337 [M$^+$]. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.47; H, 6.87; N, 3.88.

Compound **4a**: colorless needles: R_f 0.38 (hexane–EtOAc, 2:1); mp 164–165 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.47 (d, *J* = 7.6 Hz, 2 H), 7.32 (dd, J_1 = J_2 = 7.6 Hz, 2 H), 7.21 (s, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 6.74 (s, 1 H), 6.61 (s, 1 H), 4.60 (br, 1 H), 3.97 (s, 3 H), 3.89 (s, 3 H), 3.27 (br, 1 H), 3.13 (br, 1 H), 2.66 (br, 1 H), 1.02 (s, 9 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.3, 149.3, 147.7, 137.2, 134.0, 128.4, 128.3, 128.0, 126.8, 125.4, 117.6, 111.7, 106.4, 80.3, 56.2, 55.9, 43.0, 28.5, 27.7. IR ($CHCl_3$): 1682 cm^{-1}. MS (FAB): *m*/*z* = 381 [M$^+$]. Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.38; H, 7.08; N, 3.47.

Compound **4c**: colorless crystals; R_f 0.38 (hexane–EtOAc, 2:1); mp 146–147 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.46 (s, 1 H), 7.36 (d, *J* = 7.8 Hz, 1 H), 7.24 (dd, J_1 = J_2 = 7.8 Hz, 1 H), 7.18 (s, 1 H), 7.17 (d, *J* = 7.8 Hz, 1 H), 6.68 (s, 1 H), 6.61 (s, 1 H), 4.59 (br, 1 H), 3.96 (s, 3 H), 3.89 (s, 3 H), 3.26 (br, 1 H), 3.12 (br, 1 H), 2.66 (br, 1 H), 1.07 (s, 9 H). ^{13}C NMR (126 MHz, $CDCl_3$): d = 153.0, 149.5, 147.7, 139.1, 135.3, 134.2, 129.5, 128.3, 128.2, 126.7, 126.3, 125.0, 116.0, 111.7, 106.4, 80.6, 56.2, 55.9, 43.1, 28.3, 27.8. IR ($CHCl_3$): 1685 cm^{-1}. MS (FAB): *m*/*z* = 415 [M$^+$]. Anal. Calcd for $C_{23}H_{26}ClNO_4$: C, 66.42; H, 6.30; N, 3.37. Found: C, 66.38; H, 6.32; N, 3.35.