Gold Catalysis

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A Highly Efficient and Selective Au^I-Catalyzed Tandem Synthesis of Diversely Substituted Pyrrolo[1,2-*a*]quinolines in Aqueous Media**

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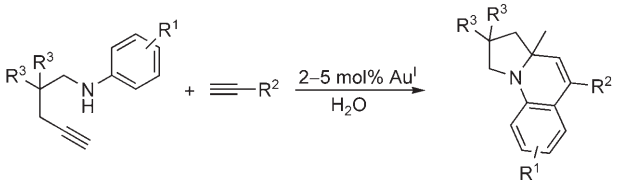
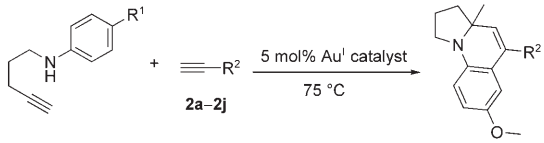
Transition-metal-catalyzed tandem carbon–carbon and carbon–heteroatom bond-forming reactions are powerful tools for the construction of multiring organic compounds because of the intriguing selectivity and high atom economy.[1] Among the numerous methods for this endeavor gold-catalyzed transformations are receiving much attention,[2,3] but examples of such reactions conducted in aqueous media are sparse.[3k,l,u] Water often exhibits an unprecedented effect on the rate and selectivity of organic reactions through hydrophobic interactions and the enrichment of organic substrates in the local hydrophobic environment.[4,5] We have recently described a Au^I-catalyzed tandem hydroamination/hydroarylation reaction of aromatic amines and alkynes in acetonitrile or nitromethane.[6] During the course of the study, we observed a gold(I)-catalyzed tandem cyclization of 1,4-aminoalkynes with alkynes in water to expediently afford diversely substituted pyrrolo[1,2-*a*]quinolines; the reaction features the formation of two new carbon–carbon bonds and one new carbon–nitrogen bond to make two rings in a one-pot reaction with high yields in aqueous solution (Scheme 1). Such reactions are particularly challenging because the regio- and chemoselectivity of alkyne C–H activation must be well-controlled to avoid formation of intractable mixtures of regioisomeric homo- and heterocoupled compounds. Substituted pyrrolo[1,2-*a*]quinolines and their oxidized or reduced forms are widespread among natural products and biologically active pharmaceuticals.[7]



Scheme 1. Synthesis of diversely substituted pyrrolo[1,2-*a*]quinolines.

To identify optimal reaction conditions for the gold-catalyzed tandem synthesis of pyrrolo[1,2-*a*]quinolines, a number of Au^I, Ag^I, and Au^{III} catalysts and different organic solvents at 60–75 °C were attempted for the reaction of 4-methoxy-*N*-(pent-4-ynyl)aniline (**1A**) with phenylacetylene (**2a**). In all cases, pyrrolo[1,2-*a*]quinoline derivative **3Aa** was obtained in low yields and poor regio- and chemoselectivities (Table 1, entries 1–4, and see the Supporting Information,

Table 1: Optimization of the reaction conditions and the scope of the reaction with respect to the alkyne.[a]



Entry	R^2	Solvent	*t* [h]	Product	Yield [%][b]
1	Ph (**2a**)	CH_3NO_2	47	**3Aa**	42
2	Ph (**2a**)	dioxane	47	**3Aa**	10
3	Ph (**2a**)	CH_3CN	47	**3Aa**	18
4	Ph (**2a**)	toluene	47	**3Aa**	59
5	Ph (**2a**)	H_2O	26	**3Aa**	87
6[c]	Ph (**2a**)	H_2O	26	**3Aa**	85
7[d]	Ph (**2a**)	H_2O	26	**3Aa**	74
8[e]	Ph (**2a**)	H_2O	26	**3Aa**	66
9[f]	Ph (**2a**)	H_2O	36	**3Aa**	86
10[g]	Ph (**2a**)	H_2O	40	**3Aa**	48
11[h]	Ph (**2a**)	H_2O	26	**3Aa**	73
12[i]	Ph (**2a**)	H_2O	18	**3Aa**	85
13	4-CH_3Ph (**2b**)	H_2O	26	**3Ab**	91 (85[j])
14	4-CH_3OPh (**2c**)	H_2O	26	**3Ac**	90 (86[j])
15	3-CH_3OPh (**2d**)	H_2O	36	**3Ad**	91
16	2-CH_3OPh (**2e**)	H_2O	30	**3Ae**	82
17	4-PhPh (**2f**)	H_2O	26	**3Af**	87 (84[j])
18	4-CF_3Ph (**2g**)	H_2O	23	**3Ag**	81 (79[j])
19	4-FPh (**2h**)	H_2O	30	**3Ah**	80 (76[j])
20	**2i**[k]	H_2O	30	**3Ai**	84
21[l]	*n*Bu (**2j**)	H_2O	45	**3Aj**	67
22[m]	Ph (**2a**)	H_2O	56	**3Aa**	91
23[n]	Ph (**2a**)	H_2O	108[n]	**3Aa**	85

[a] **1A** (0.1 mmol), **2a** (0.4 mmol), [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]Cl/$AgSbF_6$ (0.005 mmol), 75 °C. Au^I catalyst = [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]Cl/$AgSbF_6$. [b] Yield of isolated products based on **1A**. [c] **1A**/**2a**/catalyst = 1:3:0.05. [d] **1A**/**2a**/catalyst = 1:2:0.05. [e] **1A**/**2a**/catalyst = 1:1.5:0.05. [f] **1A**/**2a**/catalyst = 1:4:0.02. [g] **1A**/**2a**/catalyst = 1:4:0.01. [h] Reaction performed in the presence of air. [i] PEG 4000 (25 mg) was used as an additive. [j] **1A**/**2**/catalyst = 1:3:0.05. [k] **2i** = 1-ethynylcyclohexene. [l] **1A**/**2j**/catalyst = 1:5:0.05, 65 °C. [m] **1A** (5 mmol), **2a** (20 mmol), 5 mol% catalyst loading, H_2O (2 mL). [n] **1A** (22 mmol), **2a** (66 mmol), 2.5 mol% catalyst added in two portions (48 h + 60 h), H_2O (8 mL), 75 °C.

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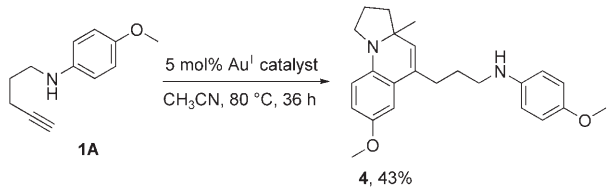
Table S1). Subsequently, we found that heating **1A** in the presence of 5 mol% of [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]Cl/AgSbF$_6$ (mol ratio = 1:1) in CH_3CN at 80 °C for 36 hours gave **4**, the product of the homocoupling of **1A** (Scheme 2). When **1A**



Scheme 2. Synthesis of **4** by homocoupling of **1A**. Au^I catalyst = [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]Cl/AgSbF$_6$.

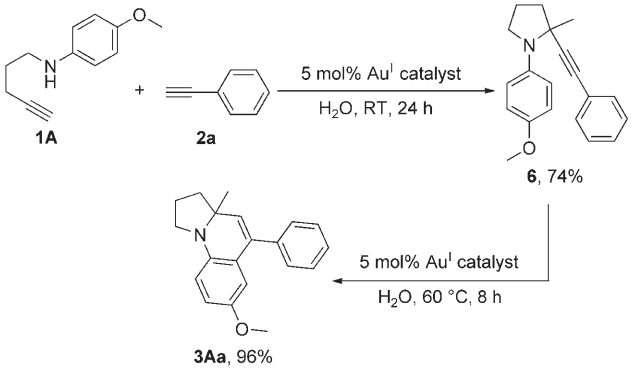
was treated with 4 equivalents of **2a** in the presence of 5 mol% of [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]Cl/AgSbF$_6$ in water at 75 °C for 26 hours, product **3Aa** was obtained exclusively in 87% yield (Table 1, entry 5). As depicted in Table 1, this reaction did not require a large excess of either reagent or careful control of reagent addition; and derivative **4** was not observed even when the amount of **2a** was reduced from 4 to 1.5 equivalents (Table 1, entries 5–8). The yield of **3Aa** remained almost the same upon decreasing the catalyst loading from 5 to 2 mol% (Table 1, entries 5 and 9). It is evident that water is instrumental to this gold-catalyzed tandem cyclization. The yield of **3Aa** was not significantly affected by the presence of air (Table 1, entry 11) and when poly(ethylene glycol) (PEG) 4000 (25 mg) was used as an additive the reaction time was shortened from 26 hours to 18 hours (Table 1, entry 12). In all cases, the excess phenylacetylene (**2a**) was converted into acetophenone after the tandem reaction and notably, CF_3SO_3H did not catalyze this reaction (see the Supporting Information, Table S1).

Under the optimized reaction conditions, we examined the substrate scope of this Au^I-catalyzed tandem cyclization in water. A variety of aromatic alkynes (4 or 3 equiv) were similarly treated with **1A** in water and the corresponding pyrrolo[1,2-*a*]quinolines **3Aa**–**Ah** were obtained in good to excellent yields (80–91%) (Table 1, entries 5, and 13–19). Compounds **3Ai** and **3Aj** were obtained in 84 and 67% yield, respectively, when 1-ethynylcyclohexene (**2i**) and 1-hexyne (**2j**) were used as the substrates (Table 1, entries 20 and 21). This protocol can be scaled up to the gram-scale synthesis of pyrrolo[1,2-*a*]quinolines. A one-pot reaction of **1A** (5 or 22 mmol) with **2a** (20 or 66 mmol) in the presence of 5 or 2.5 mol% of [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]Cl/AgSbF$_6$ afforded **3Aa** (1.3 or 5.5 g) in 91 or 85% yield, respectively, and the product was purified by simple vacuum distillation or flash chromatography (Table 1, entries 22 and 23). The [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]Cl/AgSbF$_6$ catalyst is remarkably stable and does not show appreciable decomposition after being heated in water at 75 °C for approximately 60 hours (as revealed by ^{1}H NMR spectroscopy).

A wide range of 1,4-aminoalkynes were similarly reacted with alkynes in water to furnish diversely substituted pyrrolo[1,2-*a*]quinolines (Table 2). Generally, the reaction worked well for a range of 1,4-aminoalkynes with substituents having different steric and electronic properties (Table 2, entries 1–13); however, a relatively longer reaction time was needed in the cases of *o*-OMe- and *p*-Cl-substituted 1,4-aminoalkynes (Table 2, entries 7 and 10–12). When PEG 4000 was used as an additive the reaction times were shortened from 36–42 hours to 24–27 hours with complete substrate conversion (Table 2, entries 8–11). This tandem cyclization allows rapid synthesis of tetracyclic pyrrolo[1,2-*a*]quinolines. Treatment of *N*-(pent-4-ynyl)naphthalene-1-amine (**1G**) with alkynes in water in the presence of Au[P(*t*Bu)$_2$(*o*-biphenyl)]Cl/AgSbF$_6$ furnished 1,2,3,3a-tetrahydrobenzo[*h*]pyrrolo[1,2-*a*]quinolines in 79–91% yields (Table 2, entries 14 and 15). The 1,4-aminoalkynes containing a cyclohexyl group underwent Au^I-catalyzed tandem cyclization to furnish spirocyclic pyrrolo[1,2-*a*]quinolines in 87–96% yields (Table 2, entries 16–19).

We next extended the substrate scope to other aminoalkynes. Treatment of 1,5-aminoalkyne **1J** with alkynes under the conditions described above did not give the corresponding tricyclic product. However, when AuCl alone was used as the catalyst in water, propargylamines **5Ja**, **5Jc**, and **5Jh** were exclusively afforded in 66–83% yields by using different alkynes (see the Supporting Information, Scheme S1). Subsequent reaction of **5Ja** in the presence of Au[P(*t*Bu)$_2$(*o*-biphenyl)]Cl/AgSbF$_6$ did not yield any tricyclic product, possibly attributed to the large steric hindrance during the course of intramolecular hydroarylation. Similarly, treatment of *N*-benzylpent-4-yn-1-amine (**1K**) with alkynes led to corresponding propargylamines **5Ka**, **5Kc**, and **5Kh** in 92–97% yields when 5 mol% of the AuCl catalyst was used in water (see the Supporting Information, Scheme S1).

To gain insight into the mechanism of the Au^I-catalyzed transformations, we examined the reaction of **1A** with **2a** in the presence of [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]Cl/AgSbF$_6$ at room temperature in water for 24 hours. This reaction gave propargylamine **6** in 74% yield. Subsequent treatment of **6** with [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]Cl/AgSbF$_6$ in water at 60 °C for 8 hours afforded compound **3Aa** in 96% yield (Scheme 3). On the basis of these observations, a reaction mechanism is proposed (Scheme 4). Reaction of **1** catalyzed by cationic phosphinegold(I) could generate enamine **II**. Two plausible pathways for the formation of enamine **II** can be envisioned: one proceeding by an intramolecular hydroamination[8] and the other involving the hydration of **1** to generate



Scheme 3. Propargylamine formation and cyclization. Au^I catalyst = [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]Cl/AgSbF$_6$.

Table 2: Tandem synthesis of diversely substituted pyrrolo[1,2-*a*]quinolines catalyzed by [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]Cl/AgSbF$_6$ in water.[a]

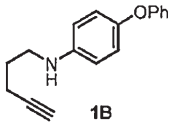
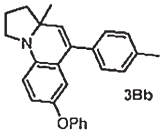
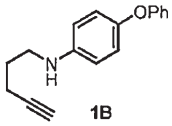
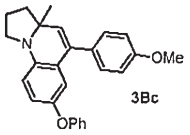
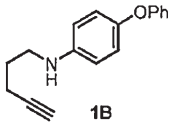
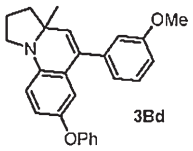
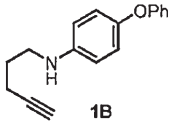
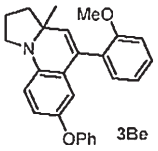
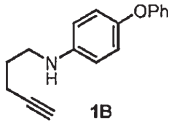
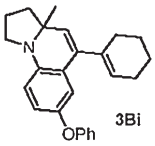
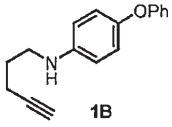
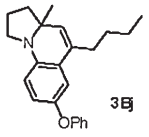
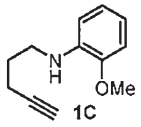
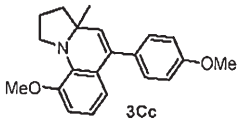
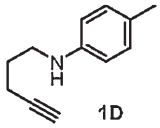
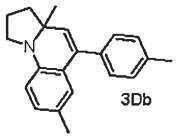
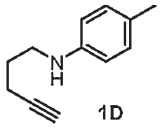
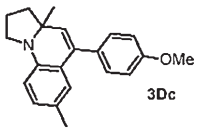
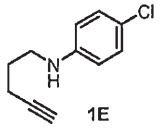
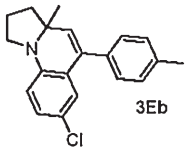
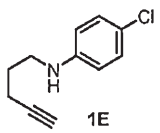
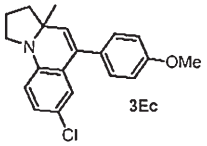
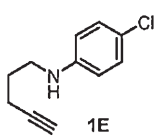
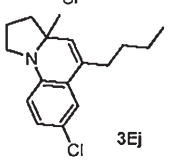
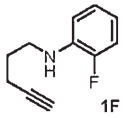
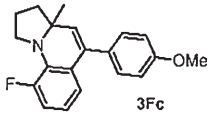
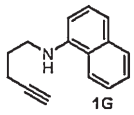
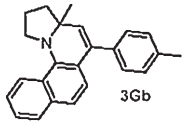
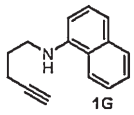
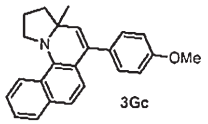
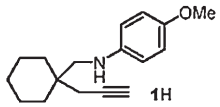
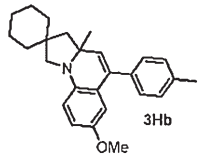
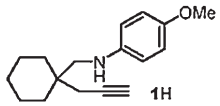
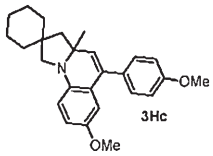
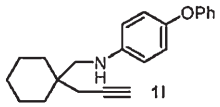
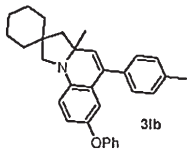
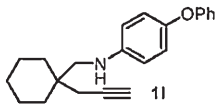
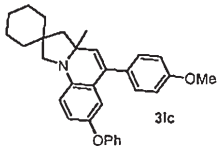
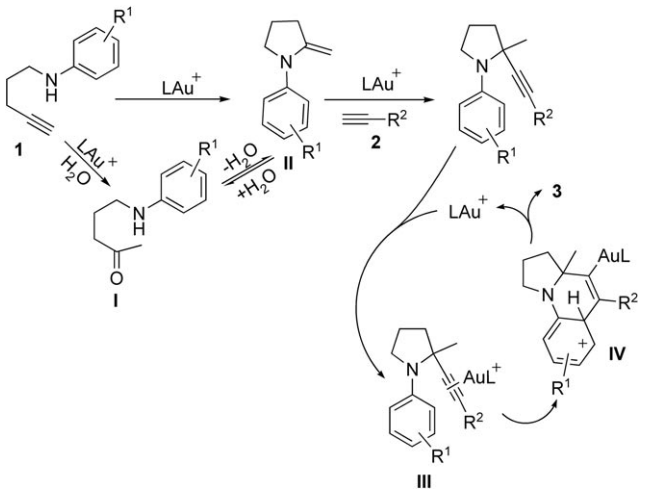
Entry	Aminoalkyne	Alkyne	*t* [h]	Product	Yield [%][b]
1	 **1B**	**2b**	24 (32[c])	 **3Bb**	97 (93[c])
2	 **1B**	**2c**	25 (32[c])	 **3Bc**	96 (98[c])
3	 **1B**	**2d**	34	 **3Bd**	92
4	 **1B**	**2e**	30	 **3Be**	90
5	 **1B**	**2i**	30	 **3Bi**	93
6[d]	 **1B**	**2j**	45	 **3Bj**	72
7	 **1C**	**2c**	56	 **3Cc**	85
8	 **1D**	**2b**	36 (24[e])	 **3Db**	89 (86[e])
9	 **1D**	**2c**	36 (26[e])	 **3Dc**	92 (89[e])
10	 **1E**	**2b**	42 (27[e])	 **3Eb**	94 (92[e])
11	 **1E**	**2c**	42 (24[e])	 **3Ec**	89 (91[e])
12[d]	 **1E**	**2j**	45	 **3Ej**	51

Table 2: (Continued)

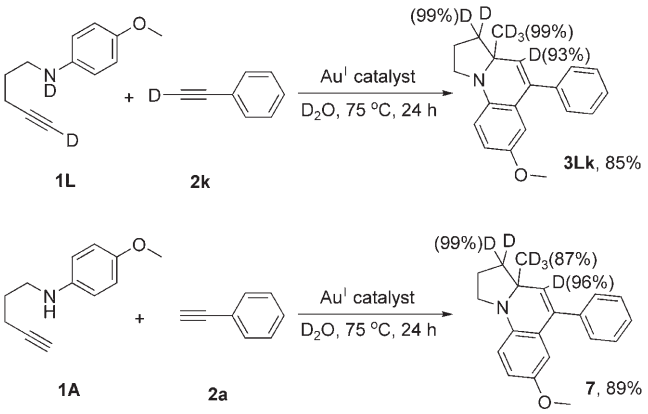
Entry	Aminoalkyne	Alkyne	*t* [h]	Product	Yield [%][b]
13	 1F	**2c**	32	 3Fc	82
14	 1G	**2b**	36	 3Gb	79
15	 1G	**2c**	36	 3Gc	91
16	 1H	**2b**	32	 3Hb	92
17	 1H	**2c**	26	 3Hc	87
18	 1I	**2b**	36 (40[c])	 3Ib	88 (87[c])
19	 1I	**2c**	36 (40[c])	 3Ic	96 (92[c])

[a] **1** (0.1 mmol), **2** (0.4 mmol), Au[P(*t*Bu)$_2$(*o*-biphenyl)]Cl/AgSbF$_6$ (0.005 mmol), H_2O (0.5 mL), 75 °C. [b] Yield of isolated product based on **1**. [c] **1**/**2**/catalyst = 1:4:0.02. [d] **1**/**2**/catalyst = 1:5:0.05, 65 °C. [e] PEG 4000 (25 mg) was used as an additive.



Scheme 4. Proposed mechanism.

ketone **I**[9,10] and intramolecular reaction of the ketone and the amine. Attack of enamine **II** by alkyne **2** would generate a propargylamine.[11] The propargylamine was cyclized intramolecularly in the presence of the gold(I) catalyst.[12] For all these steps, the proton-catalyzed reactions (if present) should not contribute significantly (see the Supporting Information, Scheme S2) despite the acidity of aquo–gold complexes.[13] Electrospray ionization mass spectrometry analysis of a solution of **6** and [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]SbF$_6$ (20 mol%) in CH_3CN after stirring for 15 minutes at room temperature showed a peak at *m*/*z* 786 that was attributed to the adduct formed between [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]$^+$ and **6**; this data supports the intermediacy of **III** depicted in Scheme 4. Labeling studies with deuterated starting materials or D_2O revealed that the vinyl hydrogen atom of **3Lk** and **7** came from D_2O (Scheme 5).[3j,q] The formation of [D_6]-**7** directly from D_2O is also consistent with the literature, in that hydrogen atoms in positions α to the enamine group can be exchanged with D_2O (Scheme 5).[3p]



Scheme 5. Labeling studies with deuterated starting materials or D_2O. Au^I catalyst = [Au{P(*t*Bu)$_2$(*o*-biphenyl)}]Cl/$AgSbF_6$.

In summary, we have developed a simple and highly efficient method for the synthesis of diversely substituted pyrrolo[1,2-*a*]quinolines with product yields up to 98% and with excellent regio- and chemoselectivities in water. The tandem sequence described here permits a straightforward and efficient synthesis of novel tri- or tetracyclic amines in which several carbon–carbon and carbon–nitrogen bonds can be formed in a one-pot reaction from simple starting materials. This method was applied in gram-scale synthesis of substituted pyrrolo[1,2-*a*]quinolines (up to 5 g). Our preliminary studies revealed that **3Bc** exhibited a significantly higher cytotoxicity against the HeLa (cervical epithelioid carcinoma) cell line (IC_{50} = 34.7 μM) than against the normal lung fibroblast (CCD-19 Lu) cell line (IC_{50} = 82.3 μM), suggesting a potential application of this class of substituted pyrrolo[1,2-*a*]quinolines in anticancer studies.

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[10] Intermediate **I** (R^1 = OMe) was detected during the course of the reaction and it was reacted with **2a** to give **6** (see the Supporting Information). Attempts to isolate **II** were not successful. Although excess **2a** was hydrolyzed to acetophenone

after the Au^{I}-catalyzed reaction, the hydration of **2** is unlikely to be involved in a pathway for the formation of **3**, since **3Aa** was not observed by treating **1 A** with acetophenone and the catalyst $[Au\{P(tBu)_2(o\text{-biphenyl})\}]Cl/AgSbF_6$ under similar reaction conditions.

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