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Diastereoselective Synthesis of α-Oxyamines *via* Gold-, Silver- and Copper-Catalyzed, Three-Component Couplings of α-Oxyaldehydes, Alkynes, and Amines in Water

Baosheng Huang,[a, b] Xiaoquan Yao,[b] and Chao-Jun Li[b,*]

[a] Applied Chemistry Research Institute, Beijing University of Chemical Technology, Beijing, People's Republic of China
[b] Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montreal, Quebec H3A 2K6, Canada
Fax: (+1)-514-398-3797; e-mail: cj.li@mcgill.ca

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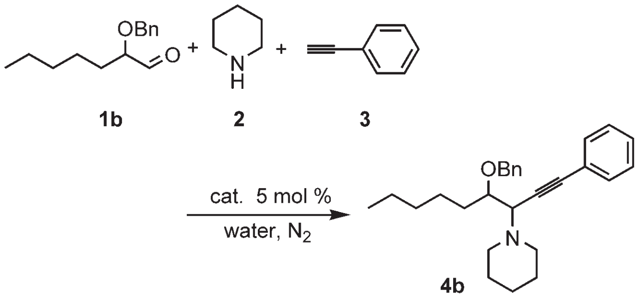
Abstract: The three-component couplings of α-oxyaldehydes, alkynes, and amines in water were investigated by using gold, silver and copper catalysts. Gold(I) was found to be the most effective catalyst in this reaction to afford propargylamines in good yields and moderate diastereoselectivities. On the other hand, silver catalysts show the best catalytic activities on non-coordinating α-alkyl-substituted aldehydes.

Keywords: alkynes; amines; gold-catalyzed; α-oxyaldehydes; reaction in water; three-component coupling

A multi-phase catalytic system in water has many potential advantages in terms of cost, safety, synthetic efficiency, operation simplicity (easy product isolation and catalyst recycling) as well as environmental concerns,[1] and it may also aid our understanding of the detailed mechanisms related to the chemistry of life.[2] Previously, we reported various highly efficient A^3-couplings (aldehyde-alkyne-amine coupling) in water catalyzed by copper, silver or gold salts.[3] The reaction generates excellent yields of the corresponding propargylamine products. Furthermore, we have also developed a highly efficient AA^3-coupling (asymmetric aldehyde, amine and alkyne coupling) in water.[3f,g]

α-Hydroxylamino derivatives are common structural units in natural products[4] and their propargyl derivatives exhibit interesting bioactivities.[5] Among the methods for preparing α-oxygen-substituted propargylamines,[6] the transition metal-catalyzed A^3-coupling is a very attractive approach due to its high efficiency and high atom-economy.[7] In order to study the scope of such reactions in complex systems such as carbohydrates, herein, we report the A^3-coupling of α-oxyaldehydes with alkynes and amines catalyzed by gold,[8] silver and copper[9] salts. Good yields and some moderate diastereoselectivities were observed in these reactions. Furthermore, an interesting chelation-acceleration effect between α-oxyaldehydes and the catalysts was also observed.

To begin our study, the couplings of α-benzoxyaldehyde **1b**, piperidine (**2**), and phenylacetylene (**3**) were examined together with various Au, Ag, and Cu salts as potential catalysts (Scheme 1 and Table 1). In our previous studies on the A^3-coupling of simple aliphatic aldehydes,[3i] silver catalysts showed much better catalytic activity than gold and copper catalysts. However, it was found that when silver(I) catalysts were used, no desired A^3 addition product was obtained in the reaction of α-benzoxyaldehydes, and cleavage of the benzyl group in the α-benzoxyaldehydes was observed from the ^{1}H NMR of the crude reaction mixture (entries 1–5). On the other hand, copper catalysts did not show any catalytic activity in the reaction under the current conditions (entries 6–10). The use of $AuBr_3$, $Au(PMe_3)Cl$, and AuCl gave excellent yields of the desired A^3-coupling product (entries 11, 13, and 14) while (*c*-hexNC)AuCl was found to be in-



Scheme 1.

Table 1. Effect of conditions on the three-component coupling of α-oxyaldehydes, piperidine and phenylacetylene.[a]

Entry	Catalyst	Solvent	Temp. [°C]	*t* [h]	yield [%][b]	*d.r.*[c]
1	AgCl	water	60	18	N.D.[e]	-
2	AgBr	water/toluene	60	18	N.D.	-
3	AgI[d]	water	60	18	0	-
4	AgI	water	60	18	0	-
5	$Ag(Ph_3P)Cl$	water	60	18	0	-
6	Cu-C≡C-Ph	water	60	18	0	-
7	CuCl	water	60	18	N.D.	-
8	CuBr	water	60	18	N.D.	-
9	CuI	water	60	18	N.D.	-
10	CuOTf/Pybox[f]	water	60	18	N.D.	-
11	$AuBr_3$	water	60	18	94	68:32
12	(*c*-hexNC)AuCl	water	60	18	N.D.	-
13	$Au(PMe_3)Cl$	water	60	18	37	73:27
14	AuCl	water	60	18	89	64:36
15	AuCl	water	r.t.	18	89	72:28
16	AuI	water	r.t.	18	100	73:27
17	AuCl	water	0	12	57	75:25
18	AuI	water	0	12	58	76:24
19	AuI	toluene	r.t.	18	88	76:24

[a] All reactions were carried out on a 0.1 mmol scale with the ratio of aldehyde/amine/alkyne = 1:1.2:1.5 in 1 mL of solvent, under N_2.

[b] Yield was determined by ^1H NMR of the crude reaction mixture.

[c] Ratio of the two diastereomers was determined by ^1H NMR analysis of the crude reaction mixtures, and absolute configuration was not determined.

[d] Solvent is a mixture of water and toluene with the ratio of 5:2, and the reaction was carried out in air.

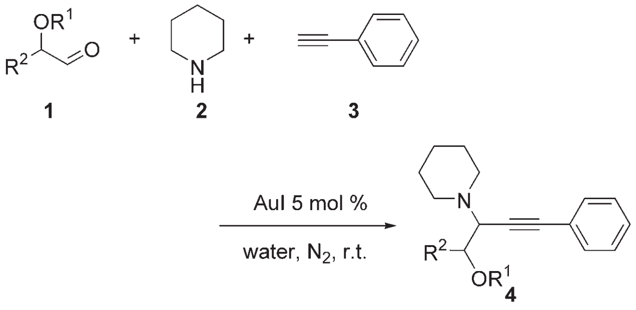
[e] N.D. = not detected.

[f] Pybox is [*S*-(*R**,*R**)]-2,6-bis(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine, (Cu:Pybox*x* = 1:1.2).

active (entry 12). Even at room temperature, the reaction catalyzed by AuCl and AuI still gave high yields of the A^3 product with moderate diastereoselectivities (entries 15 and 16). The reaction can also be carried out at 0 °C, albeit with lower yields (entries 17 and 18). Furthermore, using AuI as the preferred catalyst, the reaction performed in organic solvent resulted in no appreciable improvement in the diastereoselectivity and slightly decreased the yield of the product (entry 16 vs. entry 19).

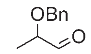
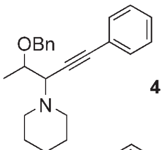
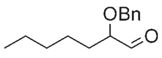
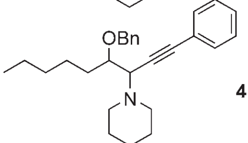
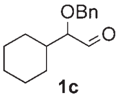
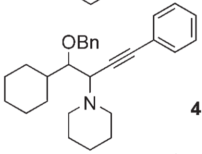
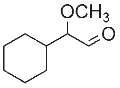
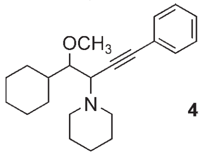
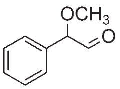
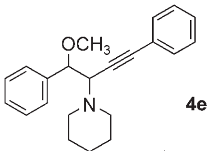
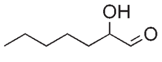
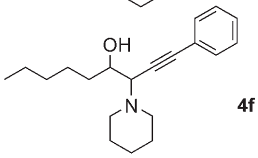
With the optimized conditions, the A^3-couplings of various α-hydroxy aldehyde derivatives were studied (Scheme 2). As can be seen from Table 2, moderate to good yields were achieved with reasonable to moderate diastereoselectivities. Compared with R^2, the protecting group R^1 did not show any obvious influence on the diastereoselectivities of the product (entries 1 and 2 *vs.* entries 3 and 4). The long chain aldehyde, **1b**, gave the best result in yield and selectivity. It is worthy of note that the aliphatic substituted compounds (**1c** and **1d**) show much better yields than the benzyl-substituted ones with similar *d.r.* (entry 4 *vs.* entry 5).

Unprotected α-hydroxy aldehyde **1f** was also effective under the current reaction conditions, although the reaction gives a lower conversion than other protected α-hydroxy aldehydes due to the dimerization



Scheme 2.

Table 2. Diastereoselectivity of AuI-catalyzed A^3 reaction of α-alkoxy aldehydes in water.[a]

Entry	Aldehyde	Product	Yield [%][b]	*d.r.*[c]
1	 **1a**	 **4a**	69	50:50
2	 **1b**	 **4b**	93	73:27
3	 **1c**	 **4c**	70	65:35
4	 **1d**	 **4d**	91	63:37
5	 **1e**	 **4e**	38	67:33
6	 **1f**	 **4f**	35	60:40

[a] All reactions were carried out on a 0.2 mmol scale with the ratio of aldehyde/amine/alkyne = 1:1.2:1.5, 5 mol% of AuI in 1 mL of water under N_2, and stirred at room temperature for 18 h.

[b] Yield of isolated product.

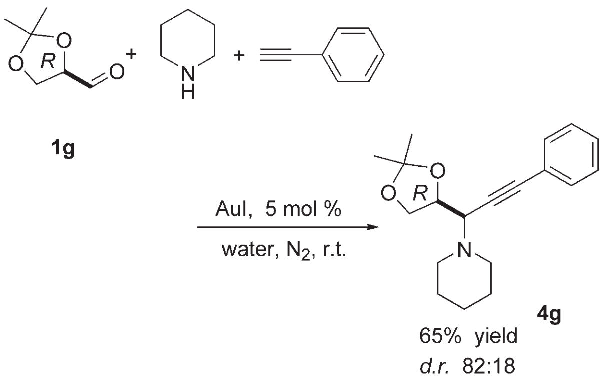
[c] Ratio of the two diastereomers was determined by ^{1}H NMR analysis of the crude reaction mixture and the absolute configurations were not determined.

of α-hydroxy aldehydes. Reasonable yield and moderate diastereoselectivity were still achieved with such unprotected hydroxy aldehydes, which provided us with opportunities to conduct further investigations on hydroxy-substituted aldehydes, especially aldehydes related to natural products and bioactive compounds.

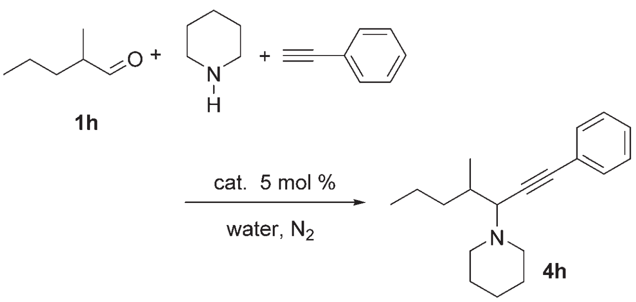
When the optically pure protected glyceraldehyde, (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde, was used, the corresponding propargylamine was obtained in high diastereoselectivity and good yield (Scheme 3).

In order to explore the origin of the diastereoselectivies in these reactions, we examined other α-alkyl-substituted aldehydes. Using the reaction of Scheme 4 as the prototype, we screened gold, silver and copper catalysts (Table 3).

Interestingly, in the absence of the α-oxy group, AgI was found to be more effective in catalyzing the A^3 reaction than gold catalysts (entry 5 *vs.* entries 1 and 2). Compared with gold catalysts, silver(I) is "harder" and easier to coordinate with the oxygen atoms in the BnO and carbonyl groups to form a che-



Scheme 3.



Scheme 4.

late structure,[10] which might activate the O–C bond in the α-position and result in the cleavage of the C–O bond in BnO group and consume the silver catalyst.

Some other α-alkyl aldehydes were also investigated in the A^3-coupling, and the results were summarized in Table 4. Higher diastereoselectivity was achieved by increasing the difference between the two substituents on the α-position of aldehydes.

In conclusion, gold-, silver- and copper-catalyzed A^3-couplings of α-oxyaldehydes, alkynes, and amines in water has been studied. In these reactions, gold and silver catalysts provide complementary results between catalyzing α-oxyaldehydes and α-alkyl aldehydes. With protected glyceraldehydes as substrate, the reaction provides an efficient access to a variety of α-oxylated propargylamines. The scope, mecha-

Table 3. Diastereoselectivity of the A^3-coupling of α-alkyl aldehydes, piperidine and phenylacetylene in water.[a]

Entry	Catalyst	Temp. [°C]	*t* [h]	Yield [%][b]	*d.r.*[c]
1	AuI	60	18	53	54:46
2	$AuBr_3$	60	18	69	56:44
3	AgCl	60	18	34	53:47
4	AgBr	60	18	44	55:45
5	AgI	60	18	83	58:42
6	AgI	25	18	40	55:45
7[d]	CuBr	60	18	12	56:44
8[d]	CuOTf	60	18	8	55:45

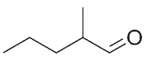
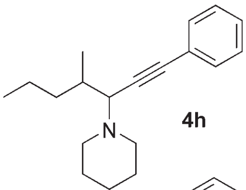
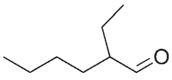
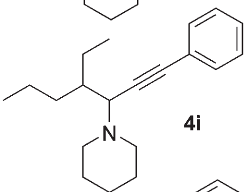
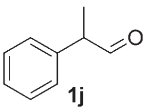
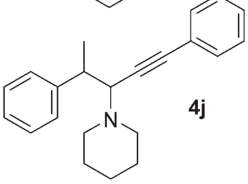
[a] All reactions were carried out on a 0.1 mmol scale with the ratio of aldehyde/amine/alkyne = 1:1.2:1.5, 1 mL of water, under N_2.

[b] Yield was determined by ^{1}H NMR of the crude reaction mixture.

[c] Ratio of two diastereomers determined by ^{1}H NMR analysis of crude reaction mixtures and absolute configuration was not determined.

[d] 10 mol% of catalyst was used.

Table 4. Diastereoselectivity of the three-component coupling of α-alkyl aldehydes, piperidine and phenylacetylene in water.[a]

Entry	Aldehyde	Product	Yield [%][b]	*d.r.*[c]
1	 **1h**	 **4h**	83	58:42
2	 **1i**	 **4i**	57	52:48[d]
3	 **1j**	 **4j**	63	71:29

[a] All reactions were carried out on a 0.2 mmol scale with the ratio of aldehyde/amine/alkyne = 1:1.2:1.5, 5 mol% of AuI, 1 mL of water under N_2.

[b] Yield of isolated product.

[c] Ratio of two diastereomers determined by ^{1}H NMR analysis of the crude reaction mixture and absolute configuration was not determined.

[d] Analyzed by GC.

nism, and synthetic application of A^3-coupling in water for other α-oxyaldehydes, such as carbohydrates, are currently under investigation.

Experimental Section

General Remarks

α-Oxyaldehydes **1a–f** (Table 2) were prepared by reported methods.[11] α-Oxyaldehyde **1g** and α-alkyl aldehydes **1h–j** (Table 4) were commercially available.

Typical Procedure for A^3-Couplings (Aldehyde-Alkyne-Amine) in Water[12]

AuI (0.0032 g, 0.01 mmol, 5 mol%) was mixed with 1 mL of distilled water, 2-(benzyloxy)propanal (**1a;** 0.0328 g, 0.2 mmol, 1 equivalent), 0.024 mL of piperidine (0.24 mmol, 1.2 equivalents) and 0.033 mL of phenylacetylene (0.3 mmol, 1.5 equivalents). The mixture was stirred at room temperature for 18 h under N_2. The reaction was stopped and extracted with ether (3×5 mL). The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel. Propargylamine **4a** was obtained in 69% yield (0.046 g).

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