ORGANIC LETTERS

2006
Vol. 8, No. 8
1529−1532

Gold(III) Salen Complex-Catalyzed Synthesis of Propargylamines via a Three-Component Coupling Reaction

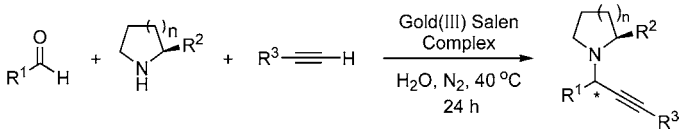
Vanessa Kar-Yan Lo, Yungen Liu, Man-Kin Wong,* and Chi-Ming Che*

Department of Chemistry and Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis, The University of Hong Kong, Pokfulam Road, Hong Kong, China

cmche@hku.hk; mkwong@hkusua.hku.hk

Received November 25, 2005

ABSTRACT



Propargylamines have been synthesized by a gold(III) salen complex-catalyzed three-component coupling reaction of aldehydes, amines, and alkynes in water in excellent yields at 40 °C. With chiral prolinol derivatives as the amine component, excellent diastereoselectivities (up to 99:1) have been attained. This coupling reaction has been applied to the synthesis of propargylamine-modified artemisinin derivatives with the delicate endoperoxide moieties remaining intact. Cytotoxicities with IC_{50} values up to 1.1 μM against a human hepatocellular carcinoma cell line (HepG2) were exhibited by these artemisinin derivatives.

Propargylamines are versatile synthetic intermediates for organic synthesis and important structural elements of natural products and therapeutic drug molecules. Traditionally, these compounds are synthesized by nucleophilic attack of lithium acetylides or Grignard reagents to imines or their derivatives.[1] However, these reagents are stoichiometric, highly moisture sensitive, and require strictly controlled reaction conditions. Besides, sensitive functionalities such as esters are not tolerated. Thus, there has been a continuing interest to develop transition-metal catalysts[2] such as iridium[3] and copper[4] for catalytic generation of metal acetylides under mild reaction conditions for propargylamine synthesis. Recently, gold salts have emerged as promising catalysts for C−C bond formation reactions through activation of alkynes.[5] In particular, it has been reported that propargylamines can be synthesized via a gold(III) salt-catalyzed three-component coupling reaction.[6]

Recently, we have developed ruthenium porphyrins as effective catalysts for multicomponent C−C bond formation reactions.[7] This multicomponent coupling strategy allows quick access to structurally diverse compounds, which greatly facilitates drug discovery processes in both academic and industrial research areas. Moreover, we have utilized gold(III) porphyrins as effective catalysts for cycloisomerization of allenones.[8]

We and others have studied the physical[9] and biological[10] properties of gold(III) salen complexes, but reports on the

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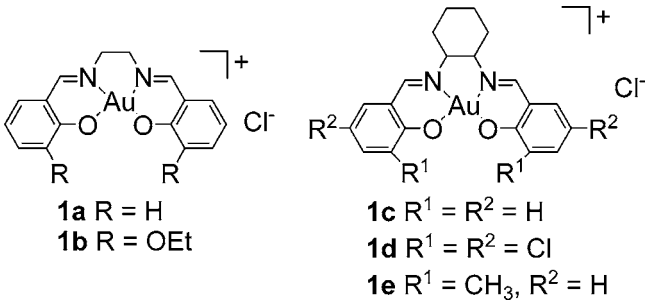
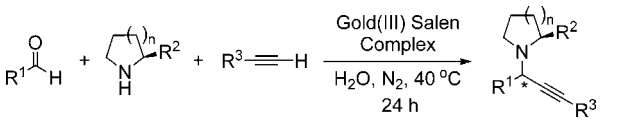
10.1021/ol0528641 CCC: $33.50
Published on Web 03/17/2006

reactivities of these complexes in catalyzing organic reactions remain sparse.[11]



Here, we report the first three-component coupling reaction of aldehydes, amines, and alkynes catalyzed by gold(III) salen complexes in water at 40 °C affording a variety of propargylamines in excellent yields (Scheme 1). When chiral

Scheme 1. Gold(III) Salen Complex-Catalyzed Three-Component Coupling Reaction

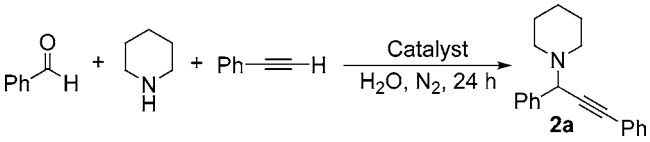


prolinol derivatives were employed as the amine component, excellent diastereoselectivity (up to 99:1) was achieved. In addition, this three-component coupling reaction has been successfully applied to the synthesis of a series of propargylamine-modified artemisinin derivatives, which were found to exhibit cytotoxicities with IC_{50} values up to 1.1 μM against a human hepatocellular carcinoma cell line (HepG2). It is worth noting that the delicate endoperoxide bridge of the artemisinin derivatives remains intact after the coupling reactions.

In the present work, five gold(III) salen complexes **1a**−**e** were synthesized and characterized according to a known literature procedure[9b] with minor modifications. In brief, **1a**−**e** were prepared by treatment of $K[Au^{III}Cl_4]$ (1 equiv) with the corresponding salen ligand (5 equiv) in refluxing CH_2Cl_2/EtOH in the presence of NH_4PF_6 (6 equiv) for 20 min (Supporting Information).

At the outset, we set out to examine the catalytic activity of **1a** in the three-component coupling reaction. The reaction was conducted by heating **1a** (0.02 mmol), benzaldehyde (2 mmol), piperidine (2.2 mmol), and phenylacetylene (3 mmol) in water (1 mL) under a nitrogen atmosphere at 40 °C for 24 h in the absence of light. On the basis of ^{1}H NMR analysis of the crude reaction mixture, 99% conversion of benzaldehyde was found, and propargylamine **2a** was isolated in 94% yield (Table 1, entry 1).[12] Reducing the catalyst loading of

Table 1. Effect of Temperature and Catalyst Screening[a]



entry	catalyst	temperature (°C)	substrate conversion (%)[b]	yield (%)[c]
1	**1a**	40	99	94
2[d]	**1a**	40	41	88
3	**1a**	room temperature	54	78
4[e]	**1a**	room temperature	78	72
5	**1b**	40	75	72
6	**1c**	40	92	90
7	**1d**	40	64	64
8	**1e**	40	35	80

[a] Catalyst/benzaldehyde/piperidine/phenylacetylene = 0.01:1:1.1:1.5. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield based on benzaldehyde conversion. [d] **1a** (0.05 mol %). [e] Reaction time was 72 h.

1a to 0.05 mol % gave **2a** with 41% conversion and 88% isolated yield (entry 2), respresenting a product TON of 820. In addition, the reactions could be performed at room temperature with good catalytic activity (54% conversion with 78% yield in 24 h, entry 3; 78% conversion with 72% yield in 72 h, entry 4).

We also examined the catalytic activities of gold(III) salen complexes **1b**−**e**. With catalyst **1b** bearing −OEt groups on the aromatic rings, a decrease in substrate conversion (75%) and yield (72%) of **2a** resulted (entry 5). Yet, for **1c** with a cyclohexylamine moiety, comparable conversion (92%) and yield (90%) with catalyst **1a** were obtained (entry 6). For **1d** (−Cl) and **1e** (−Me), a further reduction in conversions and yields resulted (entry 7 for **1d**, 64% conversion, 64% yield based on conversion; entry 8 for **1e**, 35% conversion, 80% yield based on conversion). Our findings suggest that these substituents on the aromatic rings of the salen ligands may exert unfavorable effects on the substrate conversion. On the contrary, no adverse effect was observed for **1c** bearing a cyclohexylamine moiety. Apart from gold(III) salen

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(7) (a) Li, G.-Y.; Chen, J.; Yu, W.-Y.; Hong, W.; Che, C.-M. *Org. Lett.* **2003**, *5*, 2153. (b) Li, Y.; Chan, P. W. H.; Zhu, N.-Y.; Che, C.-M.; Kwong, H.-L. *Organometallics* **2004**, *23*, 54. (c) Xu, H.-W.; Li, G.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2005**, *7*, 5349.

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complexes, we have also examined the catalytic activity of gold(III) porphyrin complexes such as [Au(TPP)Cl] (H_2TPP = *meso*-tetraphenylporphyrin). Yet, no substrate conversion was observed.

As 1 mol % of **1a** gave the best result in terms of conversion and yield within 24 h at 40 °C, these reaction conditions were adopted for subsequent studies.

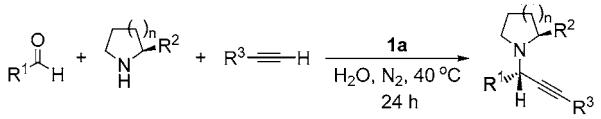
To examine the scope of this three-component coupling reaction, we extended our studies to different combinations of aldehydes, amines, and alkynes. As depicted in Table 2, this reaction works for a wide range of substrates with complete aldehyde conversion. Coupling of aromatic benzaldehyde and aliphatic cyclohexylaldehyde led to propargylamines **2a** and **2b** in 94% and 99% yields, respectively (entries 1 and 2). Both piperidine (entry 2) and pyrrolidine (entry 3) gave excellent yields (99% for **2b** and 97% for **2c**). Also, a high yield (90%) was observed for the coupling reaction of TMS-substituted alkyne (entry 4).

Coupling reactions of chiral prolinol derivatives were studied, and excellent diastereoselectivities (up to 99:1) were obtained. As shown in Table 2 (entries 5−9), the α-substituents of the prolinols play a key role on the diastereoselectivities. With ethyl prolinoate as the amine component, **2e** was obtained with a diastereomeric ratio of 84:16 in 67% yield (entry 5). Using prolinol methyl ether, **2f** was obtained with improved diastereoselectivity (95:5) in a higher yield (74%) (entry 6). The absolute configuration of **2f** was assigned with reference to the reported literature value,[4d] and those of others were assigned accordingly. Note that excellent diastereoselectivities (99:1) were obtained with prolinol in coupling with benzaldehyde to give **2g** (82% yield; entry 7) and cyclohexylaldehyde to give **2h** (89% yield; entry 8). The coupling reaction of prolinol bearing bulky diphenyl groups proceeded smoothly to afford **2i** with 99:1 dr in 83% isolated yield (entry 9). These experiments revealed that the chiral substituents on the prolinols are able to transfer chirality to the newly formed sp^3 carbon center. In addition, the ethyl ester, the methyl ether, and the hydroxyl groups remain intact after the coupling reactions.

We next examined the stability of catalyst **1a**, and experiments were conducted as follows: The coupling reaction of benzaldehyde, piperidine, and phenylacetylene was performed under the reaction conditions depicted in entry 1 of Table 2. After 24 h, the conversion was determined by ^{1}H NMR analysis of an aliquot of reaction mixture taken from the reaction flask. An additional portion of starting materials was added into the reaction mixture. Then, the reaction proceeded for an additional 24 h. The results showed that no significant loss of catalytic activity of **1a** was observed after two reaction cycles (conversion for the three successive cycles = 96%, 83%, and 73%). In addition, the reaction remained very clean without side product formation. These experiments demonstrated the recyclability of **1a**.

Artemisinin (qinghaosu, **3**), extracted from an ancient Chinese herb *Artemisia annua* (sweet wormwood), is one of the most effective antimalarial drugs (Scheme 2).[13] In the literature, there is mounting experimental evidence suggesting that the endoperoxide bridge is vital for its biological activity. Thus, a significant challenge in structural modification of

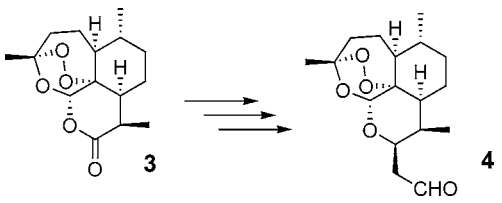
Table 2. Three-Component Coupling Reaction Catalyzed by **1a**[a]



entry	R^1	n	R^2	R^3	product	yield (%)[b]	dr[c]
1	Ph	2	H	Ph	**2a**	94	-
2	C_6H_{11}	2	H	Ph	**2b**	99	-
3	C_6H_{11}	1	H	Ph	**2c**	97	-
4	C_6H_{11}	2	H	TMS	**2d**	90	-
5[d]	Ph	1	COOEt	Ph	**2e**	67[e]	84:16
6	Ph	1	CH_2OMe	Ph	**2f**	74	95:5
7	Ph	1	CH_2OH	Ph	**2g**	82	99:1
8	C_6H_{11}	1	CH_2OH	Ph	**2h**	89	99:1
9[f]	Ph	1	$C(Ph)_2OH$	Ph	**2i**	83	99:1

[a] **1a**/aldehyde/amine/alkyne = 0.01:1:1.1:1.5. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Performed with 1.38 mmol of aldehyde with all other reagents scaled down accordingly. [e] Isolated yield based on 59% conversion. [f] Performed with 0.1 mmol of aldehyde with other reagents scaled down accordingly.

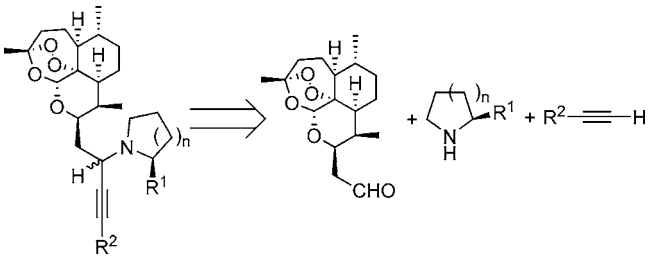
Scheme 2. Artemisinin (Qinghaosu, **3**)



artemisinins would be the choice of reagents and mild reaction conditions that do not destroy the delicate endoperoxide moiety.[14]

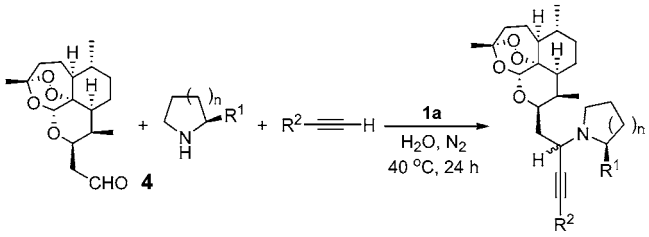
In this work, we applied the gold(III) salen complex-catalyzed three-component coupling reaction to the synthesis of new propargylamine-modified artemisinin derivatives (Scheme 3). This new coupling strategy provides a convenient access to a wider range of structurally diverse artemisinin derivatives.[15]

Scheme 3. Three-Component Coupling Reaction for Artemisinin Modification



Artemisinin aldehyde **4** prepared from **3**[14e] was used as an aldehyde component for the coupling reaction. The results of the **1a**-catalyzed (5 mol %) three-component coupling of **4** are summarized in Table 3. With piperidine and phenylacetylene, a separable mixture of **5a** and **5b** was obtained in 59% and 13% yields, respectively (entry 1). Comparable yields were obtained for **6a** (51%) and **6b** (16%) in the coupling reaction with prolinol and phenylacetylene (entry 2). For a coupling reaction with aliphatic alkyne, **7a** (29%) and **7b** (7%) were obtained (entry 3). On the basis of ^{1}H/^{13}C NMR and MS data, all the endoperoxide moieties of **5**−**7** remained intact.

Table 3. Synthesis of Propargylamine-Based Artemisinin Derivatives **5**−**7** by a Three-Component Coupling Reaction Catalyzed by **1a**[a]



entry	*n*	R^1	R^2	product	yield[b] (%)	IC_{50} (μM)
1	2	H	Ph	**5a**	59	1.1
				5b	13	5.6
2	1	CH_2OH	Ph	**6a**	51	4.3
				6b	16	9.3
3	1	CH_2OH	n-C_8H_{17}	**7a**	29	9.9
				7b	7	2.4

[a] **1a**/**4**/amine/alkyne = 0.05:1:2.2:3. [b] Isolated yield.

The in vitro cytotoxicity of **5**−**7** against a human hepatocellular carcinoma cell line (HepG2) was examined by using the MTT assay (Table 3). As illustrated, all the artemisinin derivatives displayed cytotoxicity against the HepG2 cell line with an IC_{50} value below 10 μM. The most potent cytotoxicity (IC_{50} = 1.1 μM) was exhibited by **5a**. It was interesting to note that the cytotoxicities of **5**−**7** vary with their absolute configurations and the amines/alkynes attached.

In summary, we have developed the first three-component coupling reaction of aldehydes, amines, and alkynes catalyzed by gold(III) salen complexes in water at 40 °C. A variety of propargylamines were synthesized in excellent yields, and diastereoseletivity can be up to 99:1. This coupling reaction has been applied to the synthesis of propargylamine-modified artemisinin derivatives.

Acknowledgment. We are thankful for the financial support of The University of Hong Kong (University Development Fund), Hong Kong Research Grants Council (HKU 7012/05P), and the Areas of Excellence Scheme established under the University Grants Committee of the Hong Kong Special Administrative Region, China (AoE/P-10/01).

Supporting Information Available: Experimental procedures, compound characterization data, and cytotoxicity studies of artemisinin derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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