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Gold-Catalyzed Highly Enantioselective Synthesis of Axially Chiral Allenes

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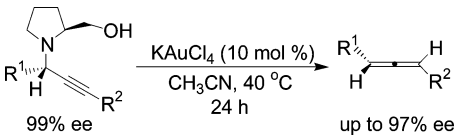
ABSTRACT



Axially chiral allenes are synthesized from chiral propargylamines catalyzed by $KAuCl_4$ in high yields (up to 93% yield) and excellent enantioselectivities (up to 97% ee) in CH_3CN at 40 °C. The reaction has been applied to the synthesis of novel allene-modified artemisinin derivatives with the delicate endoperoxide moieties remaining intact. A tentative mechanism regarding gold(I)-catalyzed intramolecular hydride transfer was proposed on the basis of deuterium-labeling experiments and ESI-MS analysis of the reaction mixture.

Allenes are important structural features of a variety of biologically active natural products.[1] The reactive orthogonal π-bonds of chiral allenes render them versatile synthons in synthetic organic chemistry.[2] The synthesis of chiral allenes mainly relies on S_N2' displacement reactions of chiral propargyl alcohols by organometallic reagents, 3,3-sigmatropic rearrangement of propargyl alcohol derivatives, and asymmetric catalysis with chiral metal complexes.[3] In view of the importance of axially chiral allenes, there has been a continuing interest in developing new methods for their synthesis under mild reaction conditions.

Gold catalysis has emerged to be an active research area in recent years.[4,5] The success of propargyl alcohols in allene synthesis prompts us to consider using chiral propargylamines for the synthesis of axially chiral allenes.[6] Our previous study showed that chiral propargylamines could be readily prepared by gold(III) salen complex-catalyzed synthesis of chiral propargylamines via a three-component coupling reaction of aldehydes, amines, and alkynes.[5b] Here, we report the unprecedented synthesis of axially chiral allenes from chiral propargylamines catalyzed by gold salts with enantiomeric excess up to 97%.[7,8]

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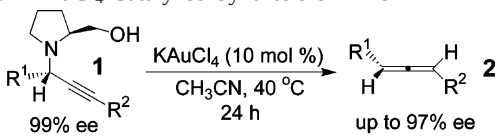
At the outset, we examined the catalytic activity of gold(III) salts toward the synthesis of chiral allene **2a** from chiral propargylamine **1a** (99% ee) (Table 1, entry 1; see also Table S1 in Supporting Information). The reaction was conducted by heating $KAuCl_4$ (0.01 mmol) and **1a** (0.1 mmol) in CH_3CN (2 mL) at 40 °C for 24 h. On the basis of ^1H NMR analysis of the crude reaction mixture, (*R*)-1,3-diphenylpropa-1,2-diene (**2a**) was formed and subsequently isolated in 82% yield based on 91% conversion. The ee value of **2a** was 93%, revealing an almost complete center-to-axis chirality transfer from **1a** to **2a**. A slight increase in enantioselectivity (95% ee) could be achieved when the reaction was conducted at room temperature, or using water as the solvent. A combination of $KAuCl_4$/AgOTf could also lead to **2a** in 83% ee. [Au(Salen)Cl] (H_2salen = *N*,*N*-ethylenebis(salicylideneimine)) and [Au(TPP)Cl] (H_2TPP = *meso*-tetraphenylporphyrin) were found to be inactive under similar conditions. Poor substrate conversion was found for $Pd(OAc)_2$ (8%), while no conversion was observed for TfOH, $ZnCl_2$, CuBr, $CuCl_2$, $RuCl_3$, K_2PtCl_4, or $Yb(OTf)_3$.

To examine the scope of this reaction, we extended our study to chiral propargylamines bearing various functionalities (Table 1). Propargylamines **1a**−**g** were converted into (*R*)-allenes **2a**−**g** in up to 93% yield and up to 93% ee (entries 1−7). It is worth noting that the aldehyde group of **1g**, which is sensitive toward Grignard or cuprate reagents (a commonly used reagent in traditional allene synthesis from propargyl alcohols) remained intact (entry 7). Interestingly, **2b** containing the *p*-CF_3 functionality could be obtained from either propargylamine **1b** or **1h** in comparable ee values (93 vs 90%). Allenes **2i** with a biphenyl group (83% ee), **2j** with a cyclohexyl group (94% ee), and **2k** with a cyclohexenyl group (50% ee) were generated from their corresponding chiral propargylamines **1i**−**k** (entries 9−11).

(*R*,*R*)-Bis-allene **2l** could be synthesized from dipropargylamine **1l** in 97% ee (entry 12). (*S*)-**2a** in 88% ee was obtained from **1m** (the enantiomer of **1a)** (entry 13). Apart from prolinol-derived propargylamines, (methoxymethyl)-pyrrolidine-derived **1n** was converted into allene **2a** with 86% ee (entry 14). Achiral pyrrolidine-derived **1o** and **1p** were converted into racemic **2a** (entries 15−16). These results showed that the reaction is especially useful for the synthesis of axially chiral 1,3-diarylallenes. *The catalysis could be scaled up to the gram scale. Thus, in a one-pot reaction, 0.88 g of* ***1a*** *gave 0.34 g of* ***2a*** *in 90% ee for a reaction time of 24 h (83% yield based on 70% conversion).*

Table 1. $KAuCl_4$-Catalyzed Synthesis of **2** from **1**[a]



entry	substrate		product	convn[b]	yield[c]	ee[d]
1	X = H	**1a**	**2a**	91	82	93
2	X = CF_3	**1b**	**2b**	76	93	93
3	X = Cl	**1c**	**2c**	72	80	89
4	X = Br	**1d**	**2d**	95	89	74
5	X = ^{t}Bu	**1e**	**2e**	87	93	66
6	X = Br	**1f**	**2f**	73	82	89
7	X = CHO	**1g**	**2g**	87	39	83
8	X = CF_3	**1h**	**2b**	57	84	90
9	X = Ph	**1i**	**2i**	77	87	83
10		**1j**	**2j**	46	66	94
11		**1k**	**2k**	77	83	50
12		**1l**	**2l**	79	33	97
13		**1m**	(S)-**2a**	83	87	88
14		**1n**	**2a**	69	92	86
15		**1o**	**2a**	43	98	-
16		**1p**	**2a**	25	66	-

[a] Substrate/catalyst = 1:0.1, ee of **1a**−**n** = 99%. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Isolated yield based on conversion. [d] Determined by HPLC using Chiralcel-OD column.

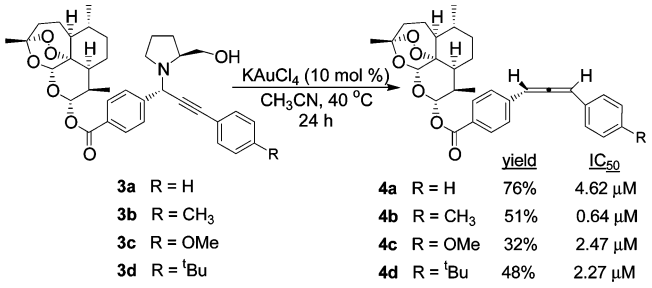
The present protocol could be applied to the modification of natural products having allene functionality. As depicted in Scheme 1, allene-modified artemisinins **4a**−**d**, which have strong cytotoxicities (IC_{50} = 0.64−4.62 μM) against a human hepatocellular carcinoma cell line (HepG2), were synthesized

(7) For palladium-catalyzed synthesis of achiral allenes from propargylamines, see: (a) Nakamura, H.; Kamakura, T.; Ishikura, M.; Biellmann, J.-F. *J. Am. Chem. Soc.* **2004**, *126*, 5958. (b) Nakamura, H.; Onagi, S.; Kamakura, T. *J. Org. Chem.* **2005**, *70*, 2357. (c) Nakamura, H.; Tashiro, S.; Kamakura, T. *Tetrahedron Lett.* **2005**, *46*, 8333. (d) Nakamura, H.; Kamakura, T.; Onagi, S. *Org. Lett.* **2006**, *8*, 2095. (e) Nakamura, H.; Onagi, S. *Tetrahedron Lett.* **2006**, *47*, 2539.

(8) During the preparation of this manuscript, Bertrand's group reported a cross-coupling of enamines and alkynes catalyzed by Au(I) to yield achiral allenes, see: (a) Lavallo, V.; Frey, G. D.; Kousar, S.; Donnadieu, B.; Bertrand, G. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 13569. For previous copper-catalyzed synthesis of achiral allenes via cross coupling of formaldehyde and alkynes in the presence of diisopropylamine, see: (b) Crabbé, P.; André, D.; Fillion, H. *Tetrahedron Lett.* **1979**, *20*, 893.

(9) For selected examples on the reduction of gold(III) by amines, see: (a) Aslam, M.; Fu, L.; Su, M.; Vijayamohanan, K.; Dravid, V. P. *J. Mater. Chem.* **2004**, *14*, 1795. (b) Newman, J. D. S.; Blanchard, G. J. *Langmuir* **2006**, *22*, 5882.

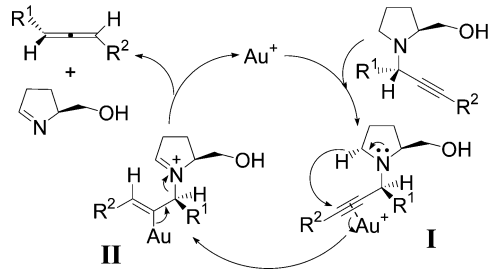
Scheme 1. Synthesis of Allene-Modified Artemisinins **4a**−**d**



as single diastereomers.[5b] The delicate endoperoxide moieties remained intact during the course of reaction.

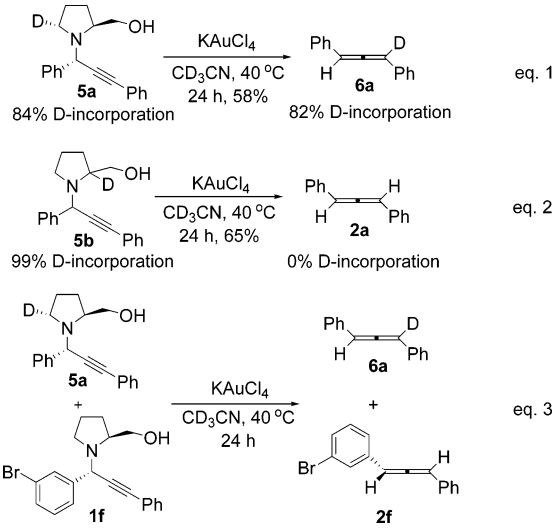
A tentative mechanism is depicted in Scheme 2. The Au(III) salt ($AuCl_4^-$) is first reduced to Au(I), possibly by an amine moiety of the substrate.[9] Au(I) generated in situ coordinates to the C−C triple bond to give intermediate **I**. The reaction mixture of **1a** and $KAuCl_4$ (10 mol %) was analyzed by ESI-MS, after stirring at rt for 1 h in CH_3CN. A peak at *m*/*z* 488.2 attributable to the adduct of **1a** and Au(I) was identified, supporting Au(I) possibly being a reactive species. Moreover, the same ee value of (*R*)-allene **2a** (93%) was obtained from the reaction of **1a** individually catalyzed by $KAuCl_4$ or AuCl, in the latter case, albeit 30% of AuCl was needed. The gold residue left after the reaction was suggested to be Au(0) by XRD analysis.

Scheme 2. Tentative Mechanism for Gold-Catalyzed Synthesis of Axially Chiral Allenes



To provide insight into the subsequent steps from **I**, deuterium-labeling experiments were performed. The findings are depicted in Scheme 3. Deuterium-labeled **5a** (84% D incorporation) was treated with $KAuCl_4$ in CD_3CN under N_2 at 40 °C for 24 h. By ^1H NMR analysis, 82% D incorporation in **6a** was obtained with 58% isolated yield (eq 1). Yet no deuterium incorporation was detected in the

Scheme 3. Deuterium-Labeling Experiments



reaction of **5b** (eq 2). As no crossover of deuterium with the allenes was observed by GC−MS analysis of the reaction mixture using a 1:1 ratio of **5a** and **1f** (eq 3), the proposed hydride transfer from **I** to **II** could occur intramolecularly,[10] although we cannot exclude the possibility of transition from intermediate **I** to **II**, involving the formation of alkylideneaziridine followed by a 1,4-hydrogen migration.[11]

To conclude, we have developed the first gold-catalyzed synthesis of axially chiral allenes from chiral propargylamines, with enantiomeric excess up to 97%.

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

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(10) Attempts were not successful to detect the fate of the pyrrolidine moiety after treatment of **1a** with Au catalyst using GC−MS or ^1H NMR analysis.

(11) Inokuchi, T.; Matsumoto, S.; Tsuji, M.; Torii, S. *J. Org. Chem.* **1992**, *57*, 5023.