Homogeneous Catalysis

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Gold(I)-Catalyzed Intramolecular Enantioselective Hydroalkoxylation of Allenes**

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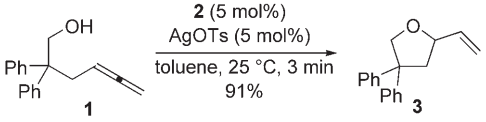
Oxygen heterocycles are components of a diverse range of naturally occurring and biologically active molecules, which include the acetogenins[1,2] and polyether antibiotics.[1,3] The widespread occurrence of oxygen heterocycles, combined with the limitations associated with the traditional methods for C–O bond formation,[1] has stimulated considerable interest in the development of new and efficient methods for the synthesis of cyclic ethers.[2–4] The addition of the O–H bond of an alcohol across a pendant C=C or C≡C bond (hydroalkoxylation) represents an attractive approach to the synthesis of cyclic ethers. Approaches based on transition metals are particularly appealing because of the potential for catalytic enantioselective hydroalkoxylation. However, despite the development of a number of processes catalyzed by transition metals for the hydroalkoxylation of C–C multiple bonds,[5] catalytic enantioselective hydroalkoxylation has not yet been demonstrated.[6]

As part of a program directed toward the development of new catalytic methods for the hydrofunctionalization of C–C multiple bonds,[7] we recently reported a highly active gold(I) catalyst for the *exo* hydroalkoxylation of γ- and δ-hydroxyallenes;[8,9] for example, reaction of the γ-hydroxyallene **1** with a catalytic 1:1 mixture of [Au{P(*t*Bu)$_2$(*o*-biphenyl)}Cl] (**2**) and AgOTs (Ts = toluene-*p*-sulfonyl) at room temperature for three minutes gave the 2-vinyltetrahydrofuran **3** in 91 % yield [Eq. (1)]. The rate, efficiency, and stereoselectivity

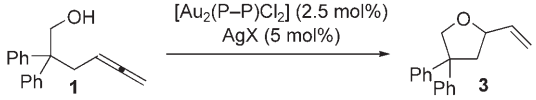


(1)

of this hydroalkoxylation pointed to the feasibility of an analogous enantioselective protocol. Herein we report the gold(I)-catalyzed enantioselective hydroalkoxylation of allenes.

Inspired by a recent report by Echavarren and coworkers,[10] and guided by our experience with gold(I)-catalyzed hydroalkoxylations,[8] we targeted Au_2 complexes of the form [Au_2(P–P)Cl_2] (P–P = 2,2′-bis(diarylphosphino)-biphenyl), activated by AgOTs, as precatalysts for the enantioselective hydroalkoxylation of allenes. Initial optimization studies identified (*S*)-**4** as an effective supporting ligand for enantioselective hydroalkoxylation (Table 1, entries 1–4). Employment of AgOTs as a cocatalyst was

Table 1: Effect of ligand and reaction conditions on the gold-catalyzed enantioselective hydroalkoxylation of **1**.



Entry	P–P[a]	Conc. **1** [mM]	Solvent	X	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	binap[d]	125	dioxane	OTs	25	2	93	19
2	(3,5-xylyl)binap	125	dioxane	OTs	25	4	84	25
3	MeO(biphep)[e]	125	dioxane	OTs	25	2	95	41
4	**4**	125	dioxane	OTs	25	2	75	86
5	**4**	125	dioxane	ClO_4	25	1	38	28
6	**4**	125	dioxane	AsF_6	25	1	36	26
7	**4**	125	dioxane	SbF_6	25	0.1	47	31
8	**4**	125	dioxane	OAc	25	17	0	–
9	**4**	125	MeOH	OTs	25	47	91	22
10	**4**	125	acetone	OTs	25	1	93	41
11	**4**	125	CH_3CN	OTs	25	2	90	44
12	**4**	125	EtOAc	OTs	25	2	75	81
13	**4**	125	THF	OTs	25	4	75	83
14	**4**	125	toluene	OTs	25	< 0.1	73	86
15	**4**	13	toluene	OTs	25	4	73	90
16	**4**	125	toluene	OTs	−20	4.5	59	94
17	**4**	63	toluene	OTs	−20	18	76	93
18	**4**	13	toluene	OTs	−20	61	73	93

[a] All ligands were of the *S* configuration. [b] Yields determined by GC against internal standard. [c] *ee* values determined by HPLC analysis on a chiral stationary phase. [d] binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl. [e] biphep = bis(phosphanyl)biphenyl.

fortuitous as the yields and enantioselectivities were significantly higher than when a range of common silver salts were used (Table 1, entries 4–8). Also noteworthy was that nonpolar solvents ($\varepsilon < 7.5$) provided considerably higher enantioselectivities than polar solvents ($\varepsilon > 20$) (Table 1, entries 4, 9–14). Toluene emerged as an attractive solvent for continued optimization because of its low melting point and the high rate of hydroalkoxylation in toluene (Table 1, entry 14). Indeed, a combination of lower reaction temperature and a twofold dilution of the reaction mixture led to improved enantioselectivity without any decrease in yield (Table 1, entry 17). In the corresponding preparative-scale reaction, treatment of **1** (63 mM) with a catalytic 1:2 mixture of

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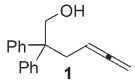
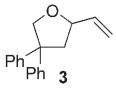
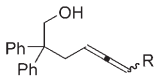
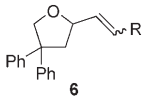
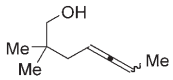
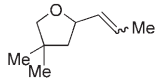
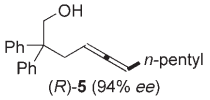
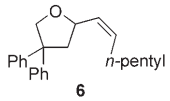
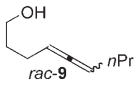
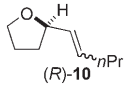
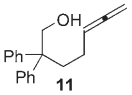
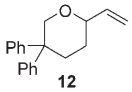
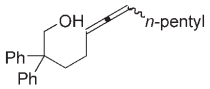
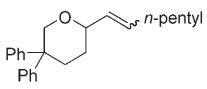
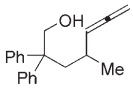
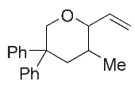
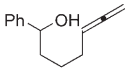
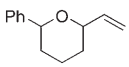
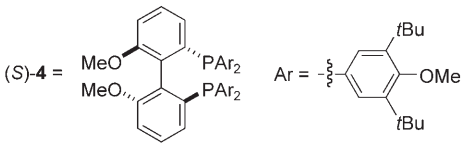
Table 2: Enantioselective hydroalkoxylation of γ- and δ-hydroxyallenes catalyzed by a 1:2 mixture of $[Au_2\{(S)\text{-}\mathbf{4}\}Cl_2]$ and AgOTs in toluene at −20 °C for 12–24 h.

Entry	Alkenyl alcohol	Product	Ratio of isomers[a]	Yield [%][b]	*ee* [%][c]
1	 **1**	 **3**	–	67	93
2	 *rac*-**5** (R = *n*-pentyl)	 **6**	1:1	94	>95/>95[d]
3	*rac*-**7** (R = Me)	**8**	1:1	96	97/99
4			1:1	95[e]	93/95
5	 (*R*)-**5** (94% *ee*)	 **6**	>20:1	88	>95[d]
6	 *rac*-**9**	 (*R*)-**10**	1.5:1	94[e]	28/39
7	 **11**	 **12**	–	96	88
8			1.5:1	92	67/93
9			1.3:1	99	81/82
10			1:3.3	95	88/45

[a] Ratio of isomers refers to *trans*/*cis* or *E*/*Z*. [b] Combined yield of all diastereomers with >95% purity. [c] For reactions that form two diastereomers, *ee* values are reported as *trans*/*cis* or *E*/*Z*. [d] Determination of the enantiomeric purity was complicated by the coelution of one enantiomer of (*E*)-**6** with one enantiomer of (*Z*)-**6** in HPLC. [e] Yield determined by ^{1}H NMR analysis with reaction carried out in $[D_8]$toluene.

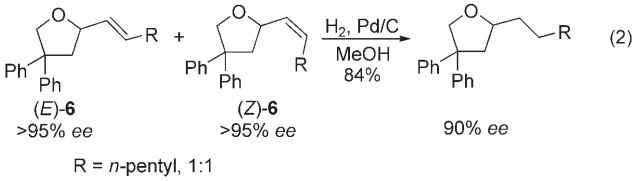
$[Au_2\{(S)\text{-}\mathbf{4}\}Cl_2]$ (2.5 mol%) and AgOTs at −20 °C for 18 hours led to isolation of **3** in 67% yield with 93% *ee* (Table 2, entry 1).[11]



γ-Hydroxyallenes that possess an axially chiral allenyl moiety were particularly effective substrates for enantioselective hydroalkoxylation (Table 2, entries 2–4). For example, reaction of *rac*-**5** with a catalytic 1:2 mixture of $[Au_2\{(S)\text{-}\mathbf{4}\}Cl_2]$ and AgOTs led to isolation of a 1:1 mixture of (*E*)- and (*Z*)-**6** (both >95% *ee*) in 94% combined yield (Table 2, entry 2). Subsequent hydrogenation of this mixture formed 2-heptyl-4,4-diphenyltetrahydrofuran in 84% yield with 90% *ee* [Eq. (2)], which thereby established that the sp^3 stereocenters of (*E*)- and (*Z*)-**6** are of the same configuration.[12] In a second experiment, the gold-catalyzed enantioselective hydroalkoxylation of (*R*)-**5** (94% *ee*) led to isolation of (*Z*)-**6** in 88% yield with greater than 95% *ee* and greater than 20:1 diastereoselectivity (Table 2, entry 5). These results indicate that the absolute configuration of the catalyst (*S*) thus determines the configuration of the sp^3 stereocenter of the product (*R*), whereas the stereochemical relationship between the catalyst and substrate determines the relative configuration about the C=C bond of the product (*S*,*S*→*E*; *S*,*R*→*Z*). Also noteworthy was that periodic analysis by HPLC on a chiral stationary phase of the gold-catalyzed cyclization of *rac*-**7** revealed that there was no significant difference in the rates with which the two enantiomers of **7** underwent enantioselective hydroalkoxylation (Figure 1).

Gold-catalyzed hydroalkoxylation of γ-hydroxyallenes tolerated dialkyl or diaryl substitution along the alkyl chain (Table 2, entries 1–5). In comparison, gold-catalyzed enantioselective hydroalkoxylation of *rac*-**9**, which possesses an unsubstituted alkyl tether, led to formation of a 1.5:1 mixture of (*R*,*E*)- and (*R*,*Z*)-**10** in excellent yield but with less than 40% *ee* (Table 2, entry 6).[13] Gold-catalyzed enantioselective hydroalkoxylation was also effective for the cyclization of both achiral and chiral δ-hydroxyallenes to form substituted tetrahydropyrans (Table 2, entries 7–10). For example, the gold-catalyzed hydroalkoxylation of **11** led to isolation of **12** in 96% yield with 88% *ee* (Table 2, entry 7).

The experiments described herein support the mechanism for the gold-catalyzed enantioselective hydroalkoxylation of *rac*-**9**



(2)

depicted in Scheme 1. In the major pathway, complexation of gold to the *Si* face of the C4=C5 bond of *rac*-**9** would form gold–allene complexes (*Si*,*S*)-**I** and (*Si*,*R*)-**I**. Outer-sphere cyclization of (*Si*,*S*)-**I** and (*Si*,*R*)-**I** would form (*R*,*Z*)-**II** and (*R*,*E*)-**II**, respectively. Deprotonation/protonolysis of (*R*,*Z*)-**II** and (*R*,*E*)-**II** with retention of stereochemistry[14] would form (*R*,*E*)-**10** and (*R*,*Z*)-**10**, respectively (Scheme 1). The minor enantiomers (*S*,*Z*)-**10** and (*S*,*E*)-**10** would be formed through outer-sphere cyclization of the gold–allene complexes (*Re*,*S*)-**I** and (*Re*,*R*)-**I**, respectively. Analogous mechanisms have been proposed for the gold-catalyzed addition of C-,[15] N-,[16] and O-nucleophiles[8,17] to alkenes and alkynes on the basis of stereochemical analysis of reaction products.

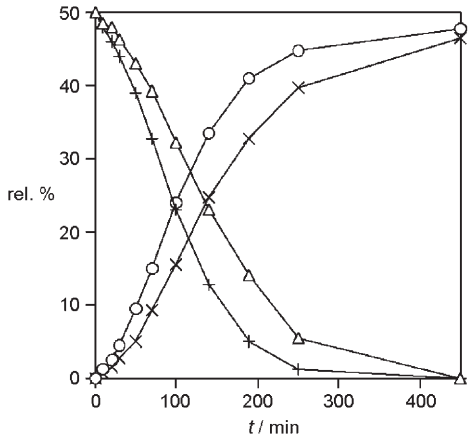
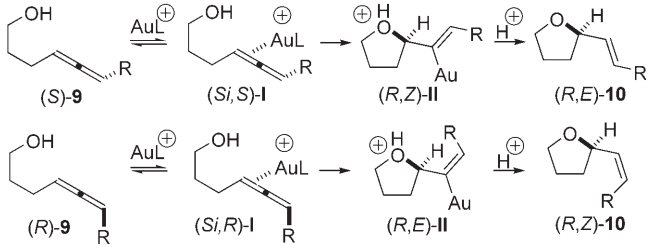


Figure 1. Plot of concentration versus time for the conversion of the two enantiomers of *rac*-**7** (+ and △) to a 1:1 mixture of (*Z*)-**8** (94% *ee*; ○) and (*E*)-**8** (96% *ee*; ×) in toluene at room temperature.



Scheme 1. Proposed mechanism for the gold-catalyzed enantioselective hydroalkoxylation of *rac*-**9**.

Experimental Section

3:[8] A mixture of $[Au_2\{(S)\text{-}\mathbf{4}\}Cl_2]$ (5.1 mg, 3.1×10^{-3} mmol) and AgOTs (1.7 mg, 6.3×10^{-3} mmol) in toluene (0.4 mL) was stirred at room temperature for 10 min. The mixture was then cooled to −20 °C and treated with a solution of **1** (31.3 mg, 0.125 mmol) in toluene (0.6 mL). The resulting suspension was stirred at −20 °C for 18 h. Column chromatography of the reaction mixture (hexanes/EtOAc 50:1→20:1) gave **3** (20.9 mg, 67%, 93% *ee*) as a colorless oil.

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[11] Control experiments ruled out the possibility of catalysis using a chiral Ag^I–phosphine complex or a chiral phosphonium salt. Treatment of **11** with a catalytic 1:1 mixture of (*S*)-**4** and either AgOTs or TsOH (5 mol%) at −20 °C for 24 h led to no detectable formation of **12** as determined by GC analysis of the crude reaction mixture.

[12] The loss of stereochemistry in the hydrogenation of (*E*)-**6** and (*Z*)-**6** presumably results from reversible opening of the allylic ether prior to hydrogenation as evidenced by the presence of traces (≤5%) of 2,2-diphenyl-1-undecanol in the reaction mixture.

[13] The absolute configuration of (*R*,*E*)-**10** and (*R*,*Z*)-**10** were determined by comparison to an authentic sample of (*R*)-**10** (*Z*/*E*=25:1, 84% *ee*) synthesized in two steps from commercially available (*R*)-tetrahydrofurfuryl alcohol.

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