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Gold(I)-Catalyzed Enantioselective Intramolecular Hydroamination of Allenes

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The number of reports on the utility of gold(I) complexes as homogeneous catalysts for organic synthesis has recently dramatically increased.[1] Despite the popularity of this area of research, only a few asymmetric reactions have been reported.[2] Within this handful of reactions, the most well-developed enantioselective gold(I)-catalyzed reaction, the Hayashi−Ito aldol,[3] proceeds via a mechanism orthogonal to the prolific area of nucleophilic addition to C−C multiple bonds. Furthermore, despite a number of reports on gold-catalyzed addition of heteroatom nucleophiles to alkynes,[4] allenes,[5] and alkenes,[6] asymmetric variants of this class of gold-catalyzed reactions have yet to be reported.[7] This challenge is not unique to gold; the asymmetric hydroamination of unactivated allenes and alkenes is a continuing goal in transition metal catalysis.[8] Phosphinegold(I) complexes are attractive catalysts for these transformations due to their inherent chemoselectivity for activation of C−C multiple bonds. However, the preferred linear geometry of gold(I) complexes places the chiral phosphine ligand distant from the reactive center, rendering enantioselective catalysis challenging.

On the basis of our previous observations,[2c] we hypothesized that chiral dinuclear gold(I)−phosphine complexes could act as efficient catalysts for the asymmetric hydroamination of allenes. To this end, tosylamine **1** was treated with mixtures of precatalyst (*R*)-3,5-xylyl-BINAP(AuCl)$_2$ (**3**) and $AgBF_4$. A species believed to be of type **C** (X = Y = BF_4, Scheme 1), generated by the treatment of precatalyst **3** with 2 equiv of $AgBF_4$, catalyzed the formation of **2** with no stereoselectivity (Table 1, entry 1). In contrast, reaction of **1** with an in situ generated monocationic catalyst[9] of type **B** (X = Cl, Y = BF_4) produced **2** in good yield with moderate enantioselectivity (entry 2). This remarkable increase in enantioselectivity[10] led us to conclude that the remaining coordinated counterion was crucial for stereoinduction. We hypothesized that replacing chloride with a larger coordinated counterion could further increase the transmission of chiral information. Employing coordinating anions, however, necessitates a complex of type **A** to be in equilibrium with catalytically active species **B**. To ensure that appreciable amounts of active catalyst are present in solution, an ideal counterion must be electronically as well as sterically modifiable. Therefore, we envisioned that a type **A** carboxylate complex (X = Y = RCO_2) could satisfy these requirements.

We were pleased to find a dramatic amplification of enantiomeric excess when benzoate counterions[11] were employed. Treating tosylamine **1** with precatalyst **3** and 2 equiv of silver benzoate[12] provided **2** with excellent (98%) ee, but was low yielding even after extended reaction times (entry 3). We theorized that the poor conversion was due to low equilibrium concentrations of the catalytically active cationic species.[13] Therefore, an electron-withdrawing group was added to the benzoate in the hopes of improving conversion. The use of silver *p*-nitrobenzoate increased the yield of **2** to 76% with no loss of enantioselectivity (entry 4). Silver 3,5-dinitrobenzoate further enhanced the yield of the reaction to 82%, but eroded stereoinduction to 95% ee (entry 5).

In order to investigate the nature of the in situ generated catalyst, we examined the mixture generated from **3** and 2 equiv of AgOPNB

Scheme 1. Dinuclear Gold(I)−Phosphine Complexes

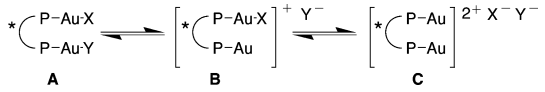
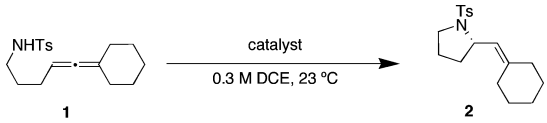


Table 1. Gold(I)-Catalyzed Asymmetric Hydroamination



entry	catalyst	time (h)	yield[a] (%)	ee[b] (%)
1	3 mol % (*R*)-xylyl-BINAP(AuCl)$_2$; 6 mol % $AgBF_4$[c]	0.5	82	1
2	3 mol % (*R*)-xylyl-BINAP(AuCl)$_2$; 3 mol % $AgBF_4$[c]	0.5	81	51
3	3 mol % (*R*)-xylyl-BINAP(AuCl)$_2$; 6 mol % AgOBz[c]	24	27	98
4	3 mol % (*R*)-xylyl-BINAP(AuCl)$_2$; 6 mol % AgOPNB[c,d]	24	76	98
5	3 mol % (*R*)-xylyl-BINAP(AuCl)$_2$; 6 mol % AgODNB[c]	17	82	95
6	3 mol % (*R*)-xylyl-BINAP(AuOPNB)$_2$ (**4**)	17	88	98
7	3 mol % (*R*)-BINAP(AuOPNB)$_2$ (**5**)	15	82	93
8	3 mol % (*S*)-BINAP(AuOPNB)$_2$ (**6**)	15	86	94[f]
9	3 mol % (*R*)-SEGPHOS(AuOPNB)$_2$ (**7**)	24	57	83
10	3 mol % (*R*)-SYNPHOS(AuOPNB)$_2$ (**8**)	24	47	92
11	3 mol % (*R*)-ClMeOBiPHEP(AuOPNB)$_2$ (**9**)	15	85	97

[a] Isolated yield after column chromatography. [b] Determined by HPLC. [c] Catalyst prepared in situ by stirring for 5 min in DCE before addition to substrate. [d] OPNB = *p*-nitrobenzoate. [e] ODNB = 3,5-dinitrobenzoate. [f] *ent*-**2**.

using ^{31}P NMR. Although we expected that (*R*)-xylyl-BINAP(AuOPNB)$_2$ (**4**) would be formed quantitatively, instead a mixture of (*R*)-xylyl-BINAP(Au_2ClOPNB)/**4**/**3** was observed.[14] We theorized the reaction would be improved by using purified **4** as the precatalyst. Gratifyingly, employing **4**, an isolable, bench-stable complex, increased the yield of **2** to 88% with a reduced reaction time, while maintaining enantioselectivity (entry 6). Importantly, a variety of BINAP and biaryl-based gold complexes (**5**−**9**)[15] were found to catalyze this transformation with good enantioselectivity (entries 7−11).[16]

The substrate scope was examined utilizing the optimized reaction conditions (Table 2).[17] The allene terminus was found to be particularly amenable to substitution. Both cyclic and linear alkanes were well tolerated (entries 1−5), yielding the corresponding pyrrolidines in good yield and excellent enantiomeric excess. Substrates with subtle electronic perturbations (entries 10 and 11) required extended reaction times and slightly elevated temperatures. The reaction could also be extended to substrates containing substitution in the tether (entries 6−9); however, in order to achieve complete conversion, these substrates required that the reaction be carried out in nitromethane at 50 °C. For example, gold(I)-catalyzed cyclization of tosylamine **18** in nitromethane at 50 °C gave

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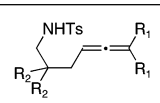
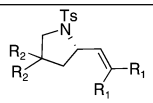
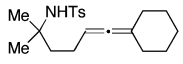
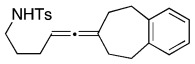
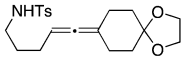
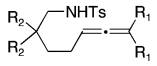
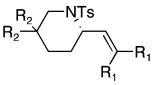
Table 2. Scope of Gold(I)-Catalyzed Hydroamination of Allenes

entry	substrate	conditions[a]	time (h)	product	% yield[b]	% ee[c]
						
1	**10** R_1 = Me; R_2 = H	A	15	**11**	98	99
2	**12** R_1 = Et; R_2 = H	A[d]	17	**13**	90	99
3	**14** R_1 = -$CH_2(CH_2)_2CH_2$-; R_2 = H	A	15	**15**	75	83
4	**1** R_1 = -$CH_2(CH_2)_3CH_2$-; R_2 = H	A	17	**2**	88	98
5	**16** R_1 = -$CH_2(CH_2)_4CH_2$-; R_2 = H	A	15	**17**	88	98
6	**18** R_1 = Me; R_2 = Me	B	15	**19**	94	93
7	**20** R_1 = Me; R_2 = -$CH_2(CH_2)_3CH_2$-	B	15	**21**	99	70
8	**22** R_1 = Me; R_2 = Ph	C	15	**23**	99	87
9	**24** 	D	17	**25**	76	96
10	**26** 	A	25	**27**	80	98
11	**28** 	A[e]	25	**29**	79	98
						
12	**30** R_1 = Me; R_2 = H	D	15	**31**	88	81
13	**32** R_1 = Et; R_2 = H	D	24	**33**	41	74
14	**34** R_1 = Me; R_2 = Me	D	24	**35**	70	98
15	**36** R_1 = Me; R_2 = Ph	D	24	**37**	70	88
16	**38** R_1 = Me; R_2 = -$CH_2(CH_2)_3CH_2$-	D	17	**39**	66	97

[a] Reaction conditions: A = 3 mol % of **4**, 0.3 M in DCE, 23 °C; B = 5 mol % of **4**, 0.3 M in $MeNO_2$, 50 °C; C = 5 mol % of **7**, 0.3 M in $MeNO_2$, 50 °C; D = 5 mol % of **9**, 0.3 M in $MeNO_2$, 50 °C. [b] Isolated yield after column chromatography. [c] Determined by HPLC. [d] 5 mol % of catalyst. [e] At 50 °C.

dimethyl-substituted pyrrolidine **19** in 94% yield and 93% ee (entry 6). While (*R*)-xylyl-BINAP(AuOPNB)$_2$ (**4**) proved the most general catalyst for the enantioselective synthesis of pyrrolidines, in some cases, additional ligand optimization was necessary. For example, the ee obtained for the cyclization of **22** to **23** improved from 53 to 87% by replacing **4** with (*R*)-SEGPHOS(AuOPNB)$_2$ (**7**) as the catalyst (entry 8). Moreover, chiral piperidines (entries 12−16) were obtained with good enantioselectivity by simply switching the catalyst to (*R*)-ClMeOBIPHEP(AuOPNB)$_2$ (**9**). For example, reaction of **38** catalyzed by 5 mol % of **9** afforded piperidine **39** in 66% yield and 97% ee.

In summary, we have uncovered a remarkable counterion effect on the enantioselectivity of gold-catalyzed intramolecular hydroamination of allenes. This discovery resulted in the development of phosphinegold(I)−bis-*p*-nitrobenzoate complexes as catalysts for enantioselective[18] formation of vinyl-substituted pyrrolidines and piperidines.[19,20] Ongoing studies into the mechanism of this reaction, application of our new chiral gold(I)−benzoate complexes to enantioselective reactions, and counterion effects on gold-catalyzed reactions will be reported in due course.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Preliminary crystallographic evidence suggests that this catalyst is polymeric in form. See Supporting Information.

(10) Efforts at modifying the noncoordinating counterion were unsuccessful. For example, 3 mol% of (*R*)-xylyl-BINAP(AuCl)$_2$/3 mol% of AgOTs produced **2** in 80% and 30% ee.

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(13) Biarylphosphine Ag(I) complexes have been previously employed as Lewis acid catalysts. See: (a) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556. However, no conversion was observed for the reaction of **1** using 5 mol% of (*R*)-xylyl-BINAP and 10 mol% of AgOPNB.

(14) ^{31}P NMR showed four signals (22.4, 21.9, 17.7, and 17.1 ppm). The assignment of these peaks to a 1:0.34:2.75 mixture of (*R*)-xylyl-BINAP-(Au_2ClOPNB)/**4**/**3** was supported by independent preparation and characterization of complexes **4** (^{31}P NMR, 17.7 ppm) and **3** (^{31}P NMR, 21.9 ppm).

(15) For a preliminary crystal structure of **9**, see Supporting Information.

(16) The use of (*R*)-xylyl-BINAP(AuOPNB)$_2$ produced **2** with similar yields and enantiomeric excess in DCM (95%, 98% ee), DCE (88%, 98% ee), and $MeNO_2$ (94%, 98% ee). Other solvents such as MeCN (48%, 98% ee), benzene (27%, 94% ee), and THF (16%, 98% ee) gave **2** with lower yields.

(17) Modifying the sulfonyl protecting group proved successful (Nosyl: 83%, 99% ee), but carbamate derivatives failed to react (Boc: <5%; Cbz: <5%).

(18) To the best of our knowledge, there has been one report of asymmetric hydroamination of allenes (maximum ee was 16%). See: Hoover, J. M.; Peterson, J. R.; Pikul, J. H.; Johnson, A. R. *Organometallics* **2004**, *23*, 4614.

(19) The absolute configuration of **15** was assigned by oxidative cleavage to *N*-*p*-toluenesulfonyl-L-(−)-proline methyl ester (see Supporting Information). The absolute configurations of the remaining products were assigned by analogy to **15**.

(20) See Supporting Information for a representative deprotection procedure.

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