

Intermolecular Hydroamination of Ethylene and 1-Alkenes with Cyclic Ureas Catalyzed by Achiral and Chiral Gold(I) Complexes

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The intermolecular hydroamination of unactivated alkenes remains an important, unsolved challenge in catalysis.¹ This transformation has been realized with alkali metal amides,² lanthanide metallocene complexes,³ or acidic zeolites,⁴ but these approaches suffer from a number of limitations, most notably poor functional group compatibility. Ru(II),⁵ Rh(III),⁶ and Pt(II)⁷ complexes catalyze the hydroamination of ethylene and, in one case, 1-hexene⁸ with carboxamides or alkyl or aryl amines, but these transformations require forcing conditions and are of extremely limited scope.⁹ Although electrophilic gold(I)-¹⁰ and platinum(II) triflate¹¹ complexes have been reported to catalyze the intermolecular hydroamination of unactivated alkenes with sulfonamides, these transformations are catalyzed with equal or greater efficiency by Brønsted acids and the metal-catalyzed reactions display behavior consistent with Brønsted acid catalysis.^{12–14} Given the challenges associated with the intermolecular hydroamination of unactivated alkenes, it is not surprising that the enantioselective intermolecular hydroamination of unactivated alkenes remains unknown.^{15,16} Here we report the Markovnikov-selective gold(I)-catalyzed hydroamination of ethylene and 1-alkenes with cyclic ureas and the unprecedented enantioselective hydroamination of unactivated 1-alkenes with up to 78% ee.

We have recently reported the room temperature intramolecular hydroamination of γ - and δ -alkenyl ureas catalyzed by a mixture of a gold(I) *N*-heterocyclic carbene (NHC) complex and AgOTf.¹⁷ The mild reaction conditions and the absence of an acid-catalyzed reaction pathway¹⁷ pointed to the potential development of a corresponding intermolecular process. However, attempts to realize the hydroamination of ethylene with acyclic ureas catalyzed by gold NHC complexes were uniformly unsuccessful. Conversely, cyclic ureas, employed in combination with a gold *o*-biphenyl phosphine precatalyst led to efficient hydroamination of ethylene. As an example, treatment of 1-methyl-imidazolidin-2-one (**1**) (0.4 M) with ethylene (120 psi) and a catalytic 1:1 mixture of (**2a**)AuCl [**2a** = P(*t*-Bu)₂*o*-biphenyl] and AgOTf (5 mol %) in dioxane at 100 °C for 20 h led to isolation of 1-ethyl-3-methyl-imidazolidin-2-one (**3**) in 99% yield (Table 1, entry 1). In addition to **1**, a number of cyclic ureas and 2-oxazolidinone reacted with ethylene at 100 °C to give the corresponding *N*-ethyl derivatives in good yield (Table 1, entries 5, 6, 7, 10).¹⁸

Extension of gold(I)-catalyzed hydroamination to include 1-alkenes was encouraging but also revealed the limitations of the (**2a**)AuCl/AgOTf catalyst system. Gold(I)-catalyzed reaction of propene or 1-butene with cyclic ureas at 100 °C led to Markovnikov hydroamination in good yield with high regioselectivity, but an extended reaction time and/or higher catalyst loading was required (Table 1, entries 2, 3, 8, 9, 11) and the method was ineffective for the hydroamination of 1-octene (Table 1, entry 4).

Continued optimization of gold(I)-catalyzed intermolecular hydroamination (Table S1) revealed that employment of AgSbF₆ as cocatalyst in combination with either (**2a**)AuCl or (**2b**)AuCl [**2b**

Table 1. Intermolecular Hydroamination of Alkenes (120 psi) with Cyclic Ureas Catalyzed by a Mixture of (**2a**)AuCl (5 mol %) and AgOTf (5 mol %) in Dioxane at 100 °C

entry	nucleophile	alkene	product	time (h)	yield ^a
		H ₂ C=CHR			
1	X = NMe (1)	R = H	3	20	99
2		R = Me		62	97
3 ^b		R = Et		69	99
4		R = (CH ₂) ₅ Me		24	38 ^c
5	X = N <i>t</i> -Bu	R = H		40	80
6	X = O	R = H		72	75
		H ₂ C=CHR			
7	n = 1	R = H		20	95
8 ^b	n = 1	R = Me		65	85
9	n = 1	R = Et		68	86 ^d
10 ^b	n = 2	R = H		19	98
11	n = 2	R = Me		67	86

^a Isolated yield of >95% purity. ^b Catalyst loading = 10 mol %. ^c ¹H NMR yield. 1-Octene loading = 10 equiv. ^d dr = 1:1.

Table 2. Intermolecular Hydroamination of Alkenes with **1** (0.4 M) Catalyzed by a Mixture of (L)AuCl (5 mol %) (L = **2a**, **2b**) and AgSbF₆ (5 mol %) in Dioxane at 100 °C

entry	alkene	alkene amt	product	L	time (h)	yield (%) ^a
	H ₂ C=CHR					
1	R = H	60 psi ^b	3	2b	24	99
2	R = Me	120 psi		2b	24	98
3	R = Et	120 psi		2b	24	96
4	R = (CH ₂) ₅ CH ₃	10 equiv		2b	24	96
5	R = (CH ₂) ₃ OH	10 equiv		2b	24	98
6	R = (CH ₂) ₃ OBn	10 equiv		2b	40	95
7	R = (CH ₂) ₂ CO ₂ H	10 equiv		2a	40	98
8	R = (CH ₂) ₄ CO ₂ Et	10 equiv		2a	40	90
9	R = Ph	15 equiv		2b	36	75
10		120 psi ^c		2a	48	72
11		20 equiv ^c		2b	70	86 ^d

^a Yield of isolated, regiochemically pure material of >95% chemical purity. ^b Reaction temperature = 60 °C. ^c Catalyst loading = 10 mol %. ^d Single diastereomer formed, relative configuration not determined.

= 2-di-*tert*-butylphosphino-1,1'-binaphthyl] in dioxane led to efficient hydroamination of ethylene and 1-alkenes with **1** (Table 2). Ethylene reacted with **1** under surprisingly mild conditions (60 psi, 60 °C, 24 h) to form **3** in 99% isolated yield (Table 2, entry 1). Likewise, gold(I)-catalyzed reaction of **1** with propene, 1-butene,

Table 3. Enantioselective Intermolecular Hydroamination of 1-Alkenes (60 equiv) with Imidazolidin-2-ones Catalyzed by a Mixture of [(*S*)-**4**](AuCl)₂ (2.5 mol %) and AgOTf (5 mol %) in *m*-Xylene at 100 °C for 48 h

entry	nucleophile	alkene	product	yield (%) ^a	ee (%) ^b
1	R = Me (1)	n = 5		86	76
2	R = Ph	n = 5		80	71
3	R = 4-C ₆ H ₄ F	n = 5		81	74
4	R = <i>t</i> -Bu	n = 5		89	78
5	R = Me (1)	n = 7		83	73
6	R = Me (1)	n = 9		76	75

(S)-4

^a Yield of isolated, regiochemically pure material of >95% chemical purity. ^b Enantiopurity determined by HPLC analysis employing chiral stationary phase.

or 1-octene was complete within 24 h to form the corresponding Markovnikov hydroamination products in >95% yield as a single regioisomer (Table 2, entries 2–4).¹⁸ Gold(I)-catalyzed intermolecular hydroamination was also effective for 1-alkenes that contained a distal hydroxyl, benzyloxy, carboxylic acid, or carboxylic ester moiety (Table 2, entries 5–8). Styrene, isobutylene, and norbornene also underwent gold-catalyzed hydroamination with **1**, albeit with diminished efficiency (Table 2, entries 9–11). Unstrained internal alkenes and α -substituted 1-alkenes failed to undergo efficient gold(I)-catalyzed intermolecular hydroamination under these conditions.

The efficient and highly regioselective hydroamination of unactivated 1-alkenes catalyzed by gold(I) phosphine complexes supported the feasibility of enantioselective intermolecular hydroamination. Indeed, a screen of enantiomerically pure bis(gold) phosphine complexes and achiral silver salts (Tables S2 and S3) led to identification of [(*S*)-**4**](AuCl)₂ [(*S*)-**4** = (*S*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP] in combination with AgOTf as an effective catalyst system for the enantioselective hydroamination of 1-alkenes with imidazolidin-2-ones (Table 3).¹⁹ For example, reaction of **1** with 1-octene (60 equiv) catalyzed by a mixture of [(*S*)-**4**](AuCl)₂ (2.5 mol %) and AgOTf (5 mol %) in *m*-xylene at 100 °C for 48 h led to the isolation of 1-methyl-3-(octan-2-yl)imidazolidin-2-one in 86% yield with 76% ee (Table 3, entry 1);¹⁸ lower octene loading led to diminished enantioselectivity. A number of 1-substituted imidazolidin-2-ones reacted with 1-alkenes in the presence of [(*S*)-**4**](AuCl)₂/AgOTf to form the corresponding Markovnikov hydroamination products in good yield with 71–78% ee (Table 3, entries 2–6).

In summary, we have developed a mild and efficient gold(I)-catalyzed protocol for the intermolecular hydroamination of ethylene and unactivated 1-alkenes with cyclic ureas, which proceeds at or below 100 °C with high Markovnikov regioselectivity. We have extended this methodology to include the unprecedented enantioselective hydroamination of unactivated 1-alkenes in good yield with up to 78% ee. We continue to work toward the development

of more general and more efficient methods for the intermolecular enantioselective hydroamination of unactivated alkenes.

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Supporting Information Available: Experimental procedures, spectroscopic data, and scans of NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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