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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 Hydroamination 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.¹⁵¹⁶ 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 24 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 extended reaction time and/or higher catalyst loading was

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

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 AgSbF_6 as co-catalyst in combination with either (**2a**)AuCl or (**2b**)AuCl [**2b** = 2-di-*t*-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, or 1-octene was complete within 24 h to form the corresponding Markovnikov hydroamination products in >95% yield as a single regioisomers (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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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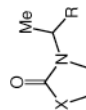
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Table 1

Catalyzed by a Mixture of (2a)AuCl (5 mol %) and AgOTf (5 mol %) in Dioxane

| alkene | product | time (h) | yield ^a |
|--------|---------|----------|--------------------|
|--------|---------|----------|--------------------|



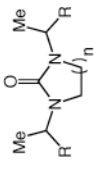
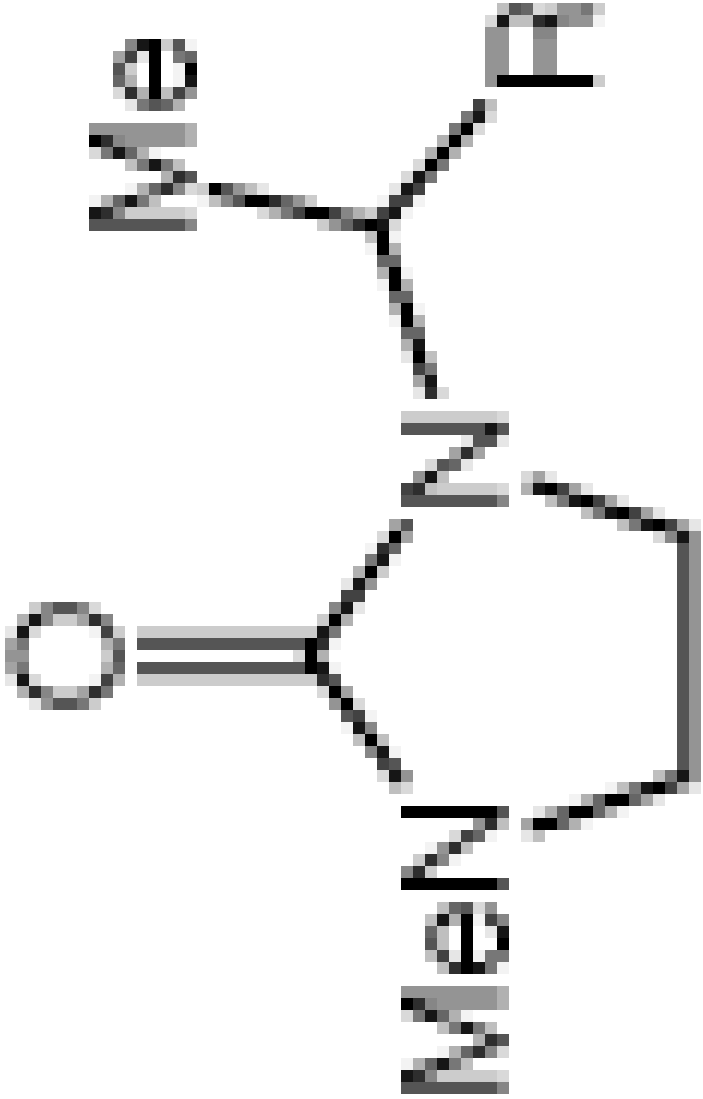

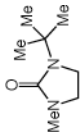
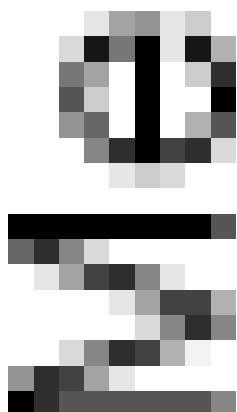
| alkene | product | time (h) | yield ^a |
|--|--|----------|--------------------|
| R = H |  <p>3</p> | 20 | 99 |
| R = Me | | 62 | 97 |
| R = Et | | 69 | 99 |
| R = (CH ₂) ₅ Me | | 24 | 38 ^c |
| R = H | | 40 | 80 |
| R = H | | 72 | 75 |
| H ₂ C=CHR | | | |
| R = H | | 20 | 95 |
| R = Me | | 65 | 85 |
| R = Et | | 68 | 86 ^d |
| R = H | | 19 | 98 |
| R = Me | | 67 | 86 |

Table 2

Reaction of a Mixture of (L)AuCl (5 mol %) (L = **2a**, **2b**) and AgSbF₆ (5 mol %) in Dioxane

| alkene amt | product | L | time (h) | yield (%) ^a |
|---------------------|---|-----------|----------|------------------------|
| 60 psi ^b |  | 2b | 24 | 99 |
| 120 psi | 3 | 2b | 24 | 98 |
| 120 psi | 3 | 2b | 24 | 96 |
| 10 equiv | 3 | 2b | 24 | 96 |
| 10 equiv | 3 | 2b | 24 | 98 |
| 10 equiv | 3 | 2b | 40 | 95 |
| 10 equiv | 3 | 2a | 40 | 98 |

| alkene amt | product | L | time (h) | yield (%) ^a |
|------------|---------|-----------|----------|------------------------|
| 10 equiv | | 2a | 40 | 90 |
| 15 equiv | | 2b | 36 | 75 |

| alkene amt | product | L | time (h) | yield (%) ^a |
|---|--|----|----------|------------------------|
|  |  | 2a | 48 | 72 |
| 120 psic | | | | |
|  | | | | |

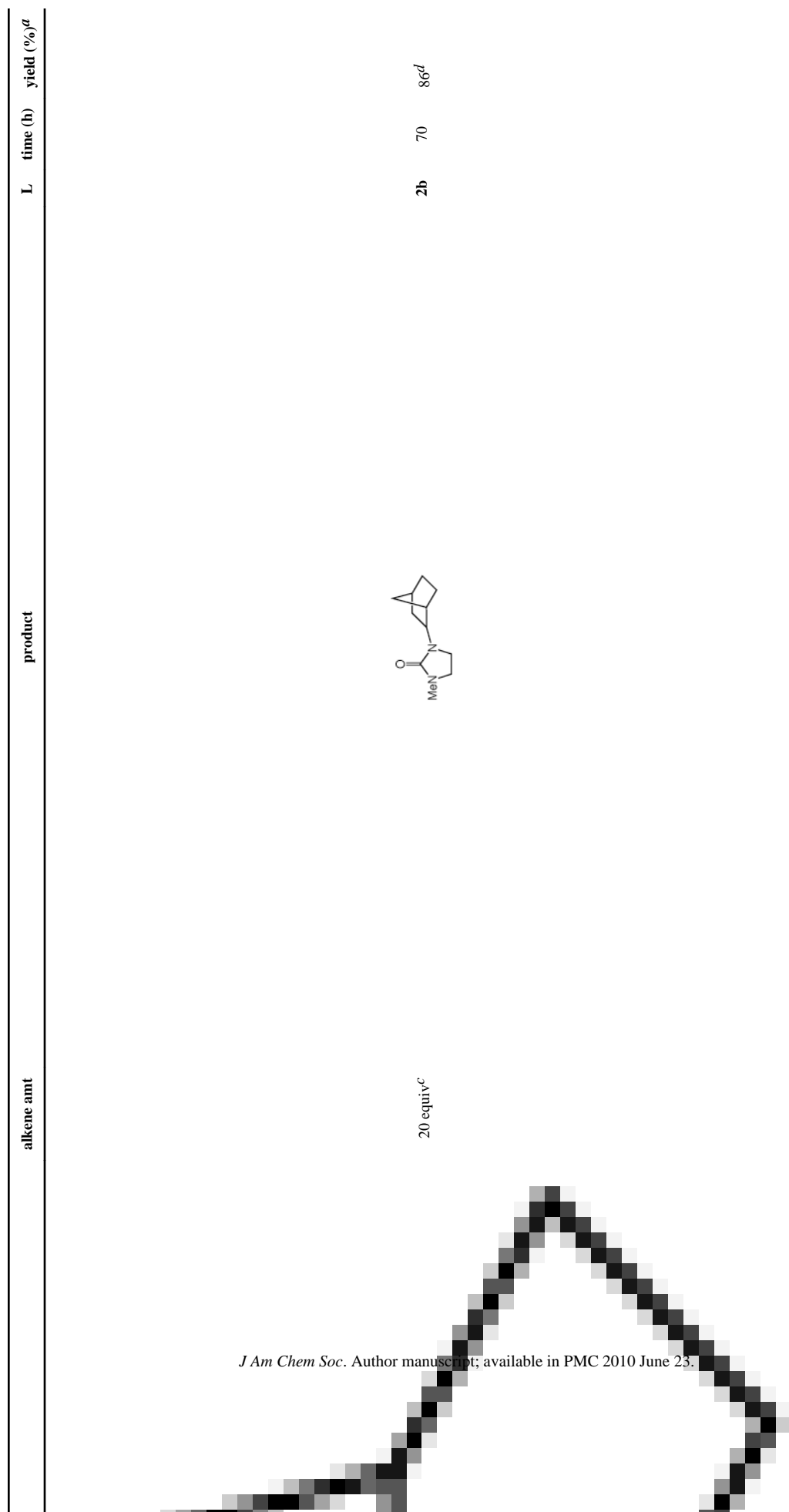


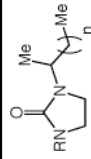
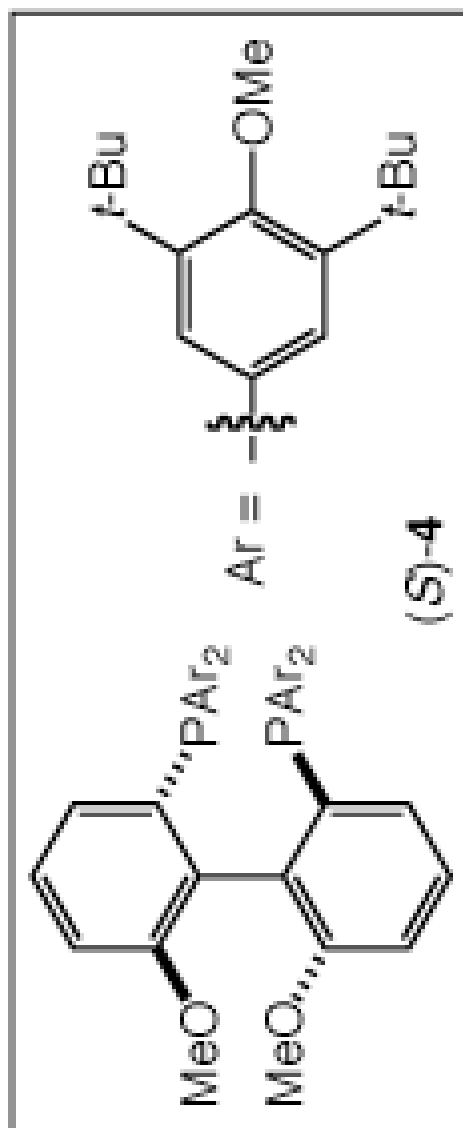


Table 3

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 | 74 |
| 6 | R = Me (1) | n = 9 | | 76 | 75 |



^aYield of isolated, regiochemically pure material of >95% chemical purity.

^bEnantiopurity determined by HPLC analysis employing chiral stationary phase.