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## Gold(I)-Catalyzed Enantioselective Intramolecular Dehydrative Amination of Allylic Alcohols with Carbamates

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### Abstract

A 1:2 mixture of [(*S*)-**2**](AuCl)<sub>2</sub> [(*S*)-**2** = (*S*)-DTBM-MeOBIPHEP] and AgClO<sub>4</sub> catalyzes the intramolecular enantioselective dehydrative amination of allylic alcohols with carbamates to form five- and six-membered aliphatic nitrogen heterocycles in high yield with up to 95% *ee*.

### Keywords

asymmetric synthesis; alcohols; amination; Au; stereoselective catalysis

The transition metal-catalyzed enantioselective amination of allylic esters and carbonates represents one of the most well established routes to the synthesis of chiral, nonracemic allylic amines.<sup>[1]</sup> With the potential to condense synthetic sequences and reduce waste streams, there has been considerable interest in the dehydrative amination of allylic alcohols as a route to enantiomerically enriched allylic amines. However, while the stereospecific amination of chiral 2°-allylic alcohols has been demonstrated,<sup>[2–4]</sup> the enantioselective amination of allylic alcohols remains problematic.<sup>[5]</sup> Carreira has reported the Ir(I)-catalyzed enantioselective amination of 1-cyclohexylprop-2-en-ol with sulfamic acid in 70% *ee*.<sup>[6]</sup> Hartwig has reported the Ir(I)/BPh<sub>3</sub>-catalyzed enantioselective intermolecular amination of 1°-allylic alcohols with aromatic amines with up to 94% *ee*, but this method was restricted to cinnamyl alcohols in the absence of a stoichiometric Lewis acid promoter.<sup>[7]</sup> Yamamoto<sup>[8]</sup> and Kitamura<sup>[9]</sup> have independently reported the enantioselective intramolecular amination of allylic alcohols catalyzed by Hg(II) and Ru(II) complexes, respectively. However, these methods were restricted to sulfonamide nucleophiles and high enantioselectivity was realized only for the formation of arene-fused nitrogen heterocycles. Here we report a gold-catalyzed protocol for the intramolecular enantioselective amination of allylic alcohols with carbamates to form five- and six-membered aliphatic nitrogen heterocycles with up to 95% *ee*.

We recently reported the intramolecular dehydrative amination of allylic alcohols with alkylamines catalyzed by an achiral gold(I) phosphine complex.<sup>[4,10]</sup> Encouraged by the high efficiency and stereospecificity of this transformation and guided by both our previous

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work in the area of gold(I)-catalyzed enantioselective allene hydroamination<sup>[11,12]</sup> and Bandini's recent demonstration of the gold(I)-catalyzed enantioselective arylation<sup>[13]</sup> and alkoxylation<sup>[14]</sup> of allylic alcohols,<sup>[15]</sup> we targeted axially chiral bis(gold) complexes as catalysts for the intramolecular enantioselective amination of the  $\gamma$ -benzylamino allylic alcohol (*E*)-**1a**. Unfortunately, optimization within this framework<sup>[16]</sup> proved largely unsuccessful and treatment of (*E*)-**1a** with a catalytic 1:2 mixture of [(*S*)-**2**](AuCl)<sub>2</sub> [(*S*)-**2** = (*S*)-DTBM-MeOBIPHEP; 2.5 mol %) and AgSbF<sub>6</sub> (5 mol %) in dioxane at 25 °C for 5 h led to quantitative conversion to 2-vinylpyrrolidine **3a**, but with only 29% *ee* (Table 1, entry 1).<sup>[17]</sup> We then focused our attention on the manipulation of the nitrogen nucleophile as a means to amplify stereoselection (Table 1). These experiments proved fruitful and gold(I)-catalyzed cyclization of Fmoc-protected  $\gamma$ -amino allylic alcohol (*E*)-**1g** employing an optimized catalyst system comprised of [(*S*)-**2**](AuCl)<sub>2</sub> (2.5 mol %) and AgClO<sub>4</sub> (5 mol %) in dioxane at room temperature for 48 h led to isolation of (*S*)-**3g** in 95% yield with 91% *ee* (Table 1, entry 7).<sup>[16,18]</sup>

The scope of gold(I)-catalyzed enantioselective intramolecular amination was evaluated as a function of alkene geometry, substitution, and ring size (Table 2). The enantioselectivity of gold(I)-catalyzed amination was sensitive to alkene geometry and gold-catalyzed cyclization of (*Z*)-**1g** formed **3g** in 99% yield with <5% *ee* (Table 2, entry 1). Although  $\gamma$ -amino allylic alcohols that possessed *gem*-dialkyl substitution at the homoallylic position cyclized with higher enantioselectivity than did an unsubstituted  $\gamma$ -amino allylic alcohol (Table 2, entries 2 – 4), homoallylic *gem*-disubstitution was not required for high enantioselectivity (Table 2, entries 5 and 6). For example, gold(I)-catalyzed cyclization of **4**, which possessed a single phenyl group at the homoallylic position, led to isolation of pyrrolidine **5** in 87% yield as ~1:1 mixture of *cis/trans* diastereomers, both of which were formed with 90% *ee*, indicative of overriding catalyst control of stereoselection. Gold-catalyzed enantioselective amination also tolerated *gem*-dialkyl substitution at the hydroxyl-bound carbon atom (Table 2, entry 7) and was applicable to the synthesis of six-membered nitrogen heterocycles, proving particularly effective for the synthesis of differentially protected 2-vinyl piperazines (Table 2, entries 8–11).

The effect of a chiral 2°-allylic alcohol moiety on the efficiency and stereoselectivity of gold-catalyzed allylic amination was evaluated employing  $\gamma$ -amino allylic alcohol **6**. In one experiment, cyclization of *rac*-**6** catalyzed by [(*S*)-**2**](AuCl)<sub>2</sub>/AgClO<sub>4</sub> led to isolation of a 1:1 mixture of (*E*)-**7** (93% *ee*) and (*Z*)-**7** (95% *ee*) in 91% combined yield (Scheme 1). Hydrogenation of this mixture formed 2-propyl pyrrolidine **8** in 92% yield with 93% *ee* (Scheme 1), which established that (*E*)-**7** and (*Z*)-**7** possessed the same absolute configuration (*S* by analogy),<sup>[18]</sup> and HPLC analysis of the conversion of *rac*-**6** to **7** revealed that both enantiomers of **6** reacted at similar rates ( $k_S/k_R = 1.06$ ). In two additional experiments, cyclization of enantiomerically enriched (*R*)-**6** (97% *ee*) catalyzed by [(*S*)-**2**](AuCl)<sub>2</sub>/AgClO<sub>4</sub> led to isolation of a 40:1 mixture of (*S,E*)-**7** (>99% *ee*) and (*R,Z*)-**7** (12% *ee*) in 93% combined yield while cyclization of (*R*)-**6** catalyzed by [(*R*)-**2**](AuCl)<sub>2</sub>/AgClO<sub>4</sub> led to isolation of 25:1 mixture (*R,Z*)-**7** (>99% *ee*) and (*S,E*)-**7** (29% *ee*) in 95% combined yield (Scheme 2). Together, these results established that asymmetric induction is determined solely by catalyst configuration (*S* → *S*; *R* → *R*) and that *E/Z* selectivity is determined by the stereochemical relationship between the incipient N-bound stereocenter and the extant O-bound stereocenter (*S/R* → *E*; *R/R* → *Z*), consistent with the net *syn* displacement of the hydroxyl group by the attacking carbamate nucleophile.

The net *syn* displacement of the hydroxyl group by the nitrogen nucleophile, which was also documented for the amination of allylic alcohols catalyzed by achiral mono(gold) complexes,<sup>[3,4]</sup> is consistent with a mechanism involving  $\pi$ -complexation of gold to the C=C bond followed by *anti*-addition of the nucleophile and *anti*-elimination of the hydroxyl

group, perhaps facilitated by an intramolecular N–H–O hydrogen bond (Scheme 3).<sup>[19]</sup> Alternatively, *syn*-substitution is also consistent with a mechanism involving  $\sigma$ -activation of the hydroxyl group followed by concerted S<sub>N</sub>2' displacement<sup>[20]</sup> and Toste has recently demonstrated that bis(gold) phosphine complexes are sufficiently Lewis acidic to acidify the hydroxyl proton of an alcohol.<sup>[21]</sup> However, the failure of either triflic acid or BF<sub>3</sub>·OEt<sub>2</sub> (10 mol %, 25 °C, 48 h) to catalyze the cyclization of (*E*)-**1g** argues against a  $\sigma$ -activation pathway for allylic amination.

In summary, we have developed a gold(I)-catalyzed protocol for the intramolecular enantioselective amination of allylic alcohols with carbamates to form five- and six-membered nitrogen heterocycles with up to 95% *ee*. Cyclization of chiral  $\gamma$ -amino allylic alcohols that possessed a stereogenic homoallylic or hydroxyl-bound carbon atom occurred with overriding catalyst control of asymmetric induction. Stereochemical analysis of the cyclization of (*R*)-**6**, which possessed a 2°-allylic alcohol moiety, established the net *syn*-displacement of the hydroxyl group by the carbamate nucleophile.

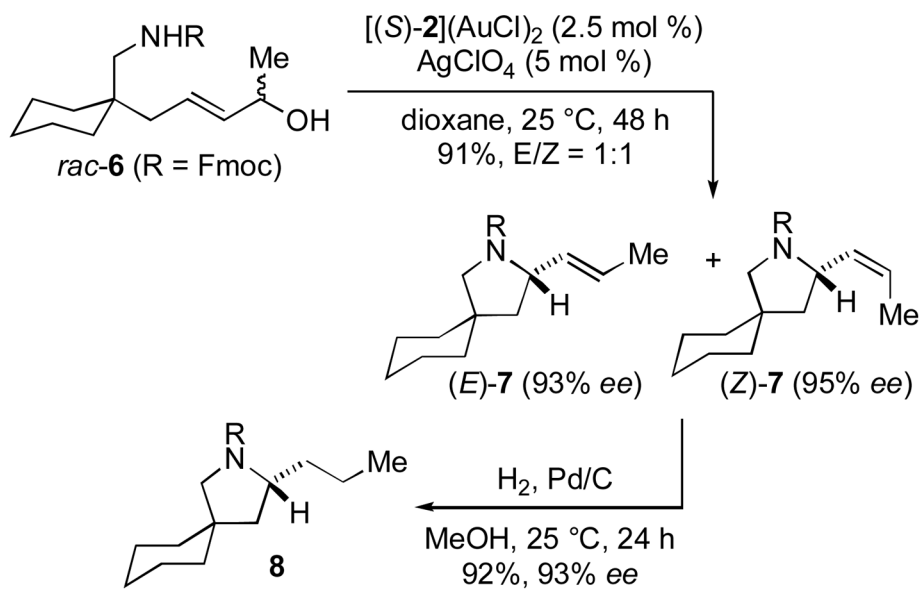
## Acknowledgments

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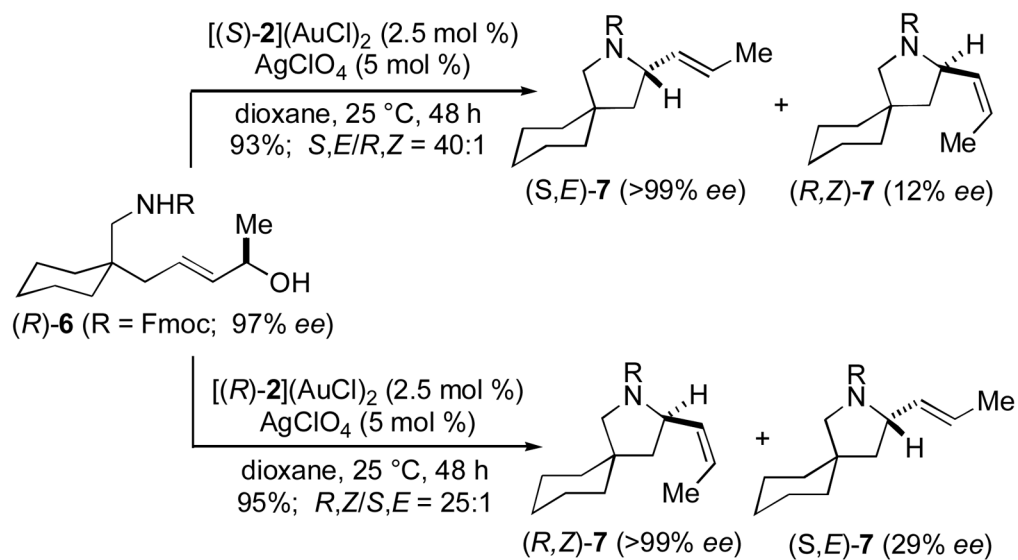
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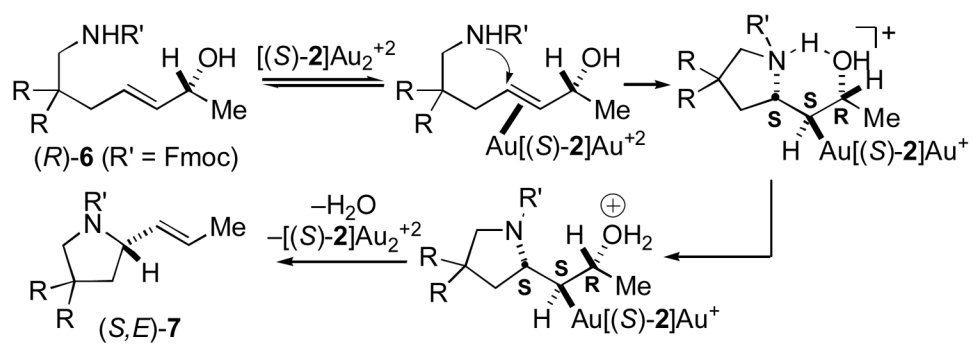
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16. A full description of optimization studies is provided in the Supporting Information.
17. Employment of a 1:1 mixture of [(*S*)-**2**](AuCl)<sub>2</sub> and AgSbF<sub>6</sub> led to significant decrease in both rate and enantioselectivity.<sup>[16]</sup>
18. The absolute configuration of (*S*)-**3b** was determined by comparison to the HPLC trace of (*R*)-**3b**.<sup>[11a]</sup> The *S* configuration of the heterocycles depicted in Table 2, entries 4 and 10 was established by chemical correlation. The absolute configurations of all other heterocycles were assigned by analogy.
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Scheme 1.



Scheme 2.



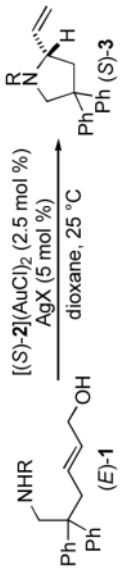
Scheme 3.

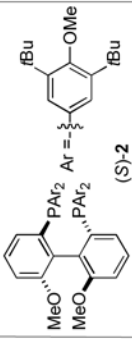
Table 1

Effect of nucleophile on the gold(I)-catalyzed intramolecular amination of allylic alcohols (*E*)-**1** under optimized conditions. [16,18]

entry	R	X	time [h]	pyrrolidine	yield [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1	Bn	SbF <sub>6</sub>	5	<b>3a</b>	100 <sup>[c]</sup>	29
2	Cbz	ClO <sub>4</sub>	48	<b>3b</b>	99	79
3	Boc	ClO <sub>4</sub>	48	<b>3c</b>	97	80
4 <sup>[d]</sup>	Troc	ClO <sub>4</sub>	48	<b>3d</b>	62	84
5	CO <sub>2</sub> Me	ClO <sub>4</sub>	48	<b>3e</b>	97	75
6	Ts	ClO <sub>4</sub>	48	<b>3f</b>	98	76
7	Fmoc	ClO <sub>4</sub>	48	<b>3g</b>	95	91





<sup>[a]</sup> Isolated yield.

<sup>[b]</sup> Determined by HPLC analysis on chiral support.

<sup>[c]</sup> Conversion.

<sup>[d]</sup> Reaction run at 40 °C.



Table 2

Substrate Scope of the Intramolecular Amination of Allylic Alcohols (0.6 M) Catalyzed by a 1:2 Mixture of [(*S*)-**2**](AuCl)<sub>2</sub> (2.5 mol %) and AgClO<sub>4</sub> (5 mol %) in Dioxane at 25 °C for 48 h.<sup>[18]</sup>

entry	substrate	heterocycle	yield [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1	 ( <i>Z</i> )- <b>1g</b>	 <b>3g</b>	95	55
2	(R = Me)		94	90
3	[R-R = -(CH <sub>2</sub> ) <sub>5</sub> -]		95	94
4	 <b>4</b> (R = Ph)	 <b>5</b>	89	62
5	 <b>4</b> (R = Ph)	 <b>5</b>	87 <sup>[c]</sup>	90/92
6	(R = <i>i</i> -Pr)		98 <sup>[c]</sup>	85/91
7	 <b>7</b>	 <b>8</b>	87 <sup>[c]</sup>	88/90
8	 <b>9</b> [R-R = -(CH <sub>2</sub> ) <sub>5</sub> -]	 <b>10</b>	69	77
9 <sup>[d]</sup>	(R <sup>1</sup> = Fmoc, R <sup>2</sup> = Boc)	 <b>11</b>	86	94
10 <sup>[d]</sup>	(R <sup>1</sup> = Fmoc, R <sup>2</sup> = Ts)		99	92
11 <sup>[d]</sup>	(R <sup>1</sup> = Boc, R <sup>2</sup> = Fmoc)		99	91

<sup>[a]</sup> Isolated yield.

<sup>[b]</sup> Determined by HPLC analysis on chiral support.

[c] Diastereomeric ratio = ~1:1.

[d] Reaction run at 50 °C.