

# Gold(I)-Catalyzed Intramolecular Amination of Allylic Alcohols With Alkylamines

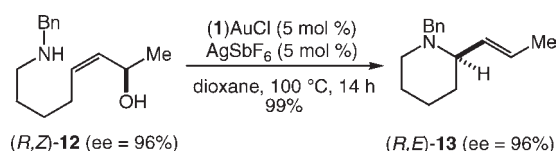
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## ABSTRACT



A 1:1 mixture of (1)AuCl [1 = P(*t*-Bu)<sub>2</sub>o-biphenyl] and AgSbF<sub>6</sub> catalyzes the intramolecular amination of allylic alcohols with alkylamines to form substituted pyrrolidine and piperidine derivatives. Gold(I)-catalyzed cyclization of (*R,Z*)-8-(*N*-benzylamino)-3-octen-2-ol (96% ee, 95% de) led to isolation of (*R,E*)-1-benzyl-2-(1-propenyl)piperidine in 99% yield with 96% ee, consistent with the net syn addition of the amine relative to the departing hydroxyl group.

In 2002, Ozawa first demonstrated the intermolecular amination of underivatized allylic alcohols without the need for a Lewis acid cocatalyst through employment of cationic palladium(II) bis(phosphine) complexes.<sup>1</sup> Since this time, a number of transition metal complexes

including Pd(0),<sup>2,3</sup> Pt(II),<sup>4</sup> Mo(VI),<sup>5</sup> Bi(III),<sup>6</sup> Au(I),<sup>7</sup> and Au(III)<sup>7</sup> have been shown to catalyze the intermolecular amination of allylic alcohols in the absence of Lewis acid activators.<sup>8</sup> Included in this family of transformations is a subset that employs simple alkylamines as nucleophiles.<sup>2,4</sup> The intramolecular amination of underivatized allylic alcohols has also attracted attention as a route to functionalized nitrogen heterocycles, and methods employing Au(III),<sup>9</sup> Bi(III),<sup>10</sup> and Pd(II)<sup>11–13</sup> catalysts in combination with carbamate or sulfonamide nucleophiles have been documented. Of these, the Pd(II)-catalyzed methods

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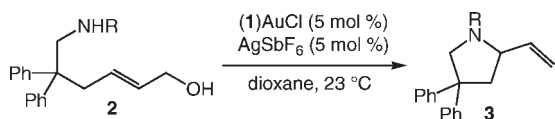
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**Table 1.** Effect of Nucleophile on the Gold(I)-Catalyzed Intramolecular Amination of Allylic Alcohols **2**



entry	R	substrate	time (h)	pyrrolidine	yield (%) <sup>a</sup>
1	Bn	<b>2a</b>	2	<b>3a</b>	97
2	<i>n</i> -Bu	<b>2b</b>	2	<b>3b</b>	96
3	<i>t</i> -Bu	<b>2c</b>	2	<b>3c</b>	87
4	H	<b>2d</b>	48	<b>3d</b>	91
5	Cbz	<b>2e</b>	72	<b>3e</b>	48
6 <sup>b</sup>	Cbz	<b>2e</b>	48	<b>3e</b>	97

<sup>a</sup> Isolated yield in >95% purity. <sup>b</sup> AgClO<sub>4</sub> used in place of AgSbF<sub>6</sub>.

are most highly developed and have been applied to the synthesis of a number of naturally occurring nitrogen heterocycles.<sup>12,13</sup> However, in contrast to the intermolecular amination of allylic alcohols, metal-catalyzed intramolecular amination of allylic alcohols with simple alkylamines has not been demonstrated.<sup>14</sup>

We have recently reported the intermolecular amination of underivatized allylic alcohols with imidazolidin-2-ones catalyzed by a mixture of (1)AuCl [**1** = P(*t*-Bu)<sub>2</sub>*o*-biphenyl] and AgSbF<sub>6</sub>, a transformation that was distinguished by the high  $\gamma$ -regioselectivity of addition in the case of unhindered allylic alcohols.<sup>15</sup> Concurrent with our efforts, Bandini and Aponick have developed effective gold(I)-catalyzed methods for the intramolecular arylation<sup>16</sup> and alkoxylation<sup>17</sup> of allylic alcohols, and these results pointed to the feasibility of gold(I)-catalyzed intramolecular allylic amination. Furthermore, Aponick's demonstration of gold(I)-catalyzed intramolecular amination of propargylic alcohols with secondary alkylamines

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(20) Control experiments established that both (1)AuCl and AgSbF<sub>6</sub> are required for efficient conversion of **2a** to **3a** and provided strong evidence against a Brønsted acid catalyzed pathway: Treatment of **2a** with either (1)AuCl (10 mol %) or HOTf (10 mol %) in dioxane at 23 °C for 24 h led to no detectable consumption of **2a** and no detectable formation of **3a**; treatment of **2a** with AgSbF<sub>6</sub> (10 mol %) in dioxane at 23 °C for 24 h led to <10% conversion to **3a**.

suggested that alkylamines might also be suitable nucleophiles for gold(I)-catalyzed intramolecular allylic amination.<sup>18,19</sup> Indeed, here we report the regio- and stereoselective gold(I)-catalyzed intramolecular amination of underivatized allylic alcohols with alkylamines.

Toward the development of a gold(I)-catalyzed protocol for the intramolecular amination of underivatized allylic alcohols with alkylamines, we targeted 6-(*N*-benzylamino)-5,5-diphenyl-2-hexenol (**2a**) in combination with the catalyst system employed for intermolecular amination. This combination proved highly efficient and treatment of **2a** with a catalytic 1:1 mixture of (1)AuCl and AgSbF<sub>6</sub> (5 mol %) in dioxane at room temperature for 2 h led to isolation of 2-vinyl pyrrolidine **3a** in 97% yield (Table 1, entry 1).<sup>20</sup> In addition to *N*-benzylamine, an *n*-butylamine (**2b**), *tert*-butylamine (**2c**), or primary amine (**2d**)

**Table 2.** Substrate Scope of the Intramolecular Amination of Allylic Alcohols Catalyzed by a 1:1 Mixture of (1)AuCl and AgSbF<sub>6</sub> (5 mol %) in Dioxane

entry	substrate	temp (°C)	time (h)	heterocycle	yield (%) <sup>a</sup>	dr <sup>b</sup>
1	<b>4a</b> (R = Bn)	23	2	<b>5a</b>	94	—
2	<b>4b</b> (R = CH(Me)Ph)	23	2	<b>5b</b>	99	2:1
3	<b>6a</b>	60	8	<b>cis-7a</b>	54	—
				<b>trans-7a</b>	41	—
4	<b>6b</b>	60	8	<b>7b</b>	99	1.5:1
5	<b>8</b> (Z/E = 7.7:1)	60	12	<b>9</b>	86	—
6	<b>10</b>	60	16	<b>11</b>	91	—
7	<b>12</b>	100	14	<b>13</b>	99	50:1
8	<b>14</b>	100	48	<b>15</b>	91	25:1

<sup>a</sup> Isolated yield in >95% purity. <sup>b</sup> Diastereomeric ratio determined by <sup>1</sup>H NMR analysis of the crude reaction mixture.

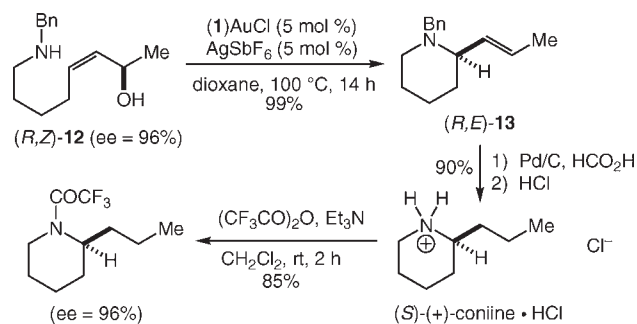
moiety also functioned as an effective nucleophile for gold(I)-catalyzed intramolecular allylic amination, although the primary amine required 48 h to reach completion (Table 1, entries 2–4). In comparison, gold(I)-catalyzed cyclization of benzyl carbamate **2e** at room temperature for 72 h formed pyrrolidine **3e** in only 48% yield (Table 1, entry 5). Substitution of  $\text{AgClO}_4$  for  $\text{AgSbF}_6$  led to a marked increase in the efficiency of the conversion of **2e** to **3e** (Table 1, entry 6), although this transformation was still considerably slower than was the gold(I)-catalyzed cyclization of substrates **2a–2c**.

We next investigated the effects of substitution, ring size, and alkene configuration on the efficiency and diastereoselectivity of gold(I)-catalyzed intramolecular allylic amination (Table 2). Cyclohexyl-substituted allylic alcohols **4a** and **4b** that possessed a benzylamine or  $\alpha$ -methylbenzyl amine nucleophile underwent intramolecular allylic amination to form piperidines **5a** and **5b**, respectively, in high yield and in the case of **4b** with modest (2:1) diastereoselectivity (Table 2, entries 1 and 2). *gem*-Dialkyl substitution along the alkyl chain that tethered the amino group to the allylic alcohol moiety facilitated intramolecular allylic amination but was not required (Table 2, entries 3–5). For example, 6-amino-2-hexenol derivative **6a** that possessed a C5 phenyl group underwent cyclization at 60 °C to form a separable 1.3:1 mixture of *cis*-**7a** and *trans*-**7a** in 95% combined yield (Table 2, entry 3). Similarly, unsubstituted 6-(*N*-benzylamino)-2-hexenol (**8**; *Z/E* = 7.7:1) underwent gold(I)-catalyzed cyclization at 60 °C to form 1-benzyl-2-vinylpyrrolidine (**9**) in 86% yield (Table 2, entry 5). Periodic analysis of the conversion of **8** to **9** by GC revealed no significant difference in the rates of cyclization of (*E*)-**8** and (*Z*)-**8**.

Gold(I)-catalyzed intramolecular allylic amination was also effective for the formation of piperidine derivatives (Table 2, entries 6–8). For example, gold(I)-catalyzed cyclization of (*Z*)-6-(*N*-benzylamino)-2-heptenol (**10**; *Z/E*  $\geq$  50:1) at 60 °C for 16 h led to isolation of 1-benzyl-2-vinylpiperidine (**11**) in 91% yield (Table 2, entry 6). Similarly, gold(I)-catalyzed cyclization of (*Z*)-8-(*N*-benzylamino)-3-octen-2-ol (**12**) at 100 °C led to isolation of 2-(1-propenyl)piperidine **13** in 99% yield with  $\geq$ 50:1 diastereoselectivity (Table 2, entry 7). Gold(I)-catalyzed cyclization of dithiane derivative **14** that possessed a stereogenic center  $\alpha$  to the amino group at 100 °C for 48 h formed *cis*-2,6-disubstituted piperidine **15** in 91% yield with 25:1 diastereoselectivity (Table 2, entry 8). Piperidine **15** represents an advanced intermediate in the synthesis of a range of naturally occurring piperidine alkaloids.<sup>21</sup>

To evaluate the selectivity of 1,3-chirality transfer in the gold(I)-catalyzed intramolecular amination of allylic alcohols with secondary alkylamines, we employed enantiomerically and diastereomerically enriched (*R,Z*)-**12** (96% ee, 95% de). Treatment of (*R,Z*)-**12** with a catalytic 1:1 mixture of (1)AuCl and  $\text{AgSbF}_6$  led to isolation of (*R,E*)-**13** in 99% yield as a single diastereomer ( $\geq$ 50:1) (Scheme

Scheme 1



1). Piperidine (*R,E*)-**13** represents a direct precursor to the naturally occurring alkaloid (*S*)-(+)-coniine, and this connection was exploited to determine both the enantiopurity and absolute configuration of (*R,E*)-**13** generated via gold(I)-catalyzed cyclization of (*R,Z*)-**12**. To this end, one-pot hydrogenative cleavage of the benzyl group and reduction of the exocyclic C=C bond (Pd/C, MeOH, HCOOH) followed by acidification with aqueous HCl gave (*S*)-(+)-coniine hydrochloride in 90% isolated yield as a white solid  $\{[\alpha]_{\text{D}}^{20} +6.9^\circ$  (*c* 0.1, EtOH); lit.  $[\alpha]_{\text{D}}^{21} +7.1^\circ$  (*c* 1.0, EtOH)}<sup>13,22</sup>. Chiral phase GC analysis of the corresponding (*S*)-(+)-coniine trifluoroacetamide (TFAA, Et<sub>3</sub>N, 85%) revealed an enantiomeric purity of 96% ee. Together, these results established the complete transfer of chirality in the conversion of (*R,Z*)-**12** to (*R,E*)-**13** and net *syn* addition of the amine relative to the departing hydroxyl group.

Although the *syn* substitution observed in the conversion of (*R,Z*)-**12** to (*R,E*)-**13** is consistent with a concerted S<sub>N</sub>2' pathway,<sup>23</sup> a mechanism involving  $\sigma$ -activation of the hydroxyl group appears unlikely given the low oxophilicity of gold(I). Rather, the pronounced  $\pi$ -acidity of cationic gold(I) complexes points to a mechanism involving nucleophilic addition/OH-elimination initiated by  $\pi$ -activation of the allylic C=C bond.<sup>24,25</sup> Within this framework, the net *syn*-substitution in the conversion of (*R,Z*)-**12** to

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(*R,E*)-**13** is consistent with either a *syn*-addition/*syn*-elimination or an *anti*-addition/*anti*-elimination sequence. Uenishi and Kawai have proposed mechanisms involving hydroxyl group-directed *syn*-addition/*syn*-elimination to account for the *syn*-substitution observed for the Pd(II)-catalyzed alkoxylation<sup>26</sup> and amination<sup>13</sup> of allylic alcohols. However, owing to the strong preference of cationic gold(I) complexes to form two-coordinate, as opposed to three-coordinate, complexes,<sup>27</sup> a mechanism involving hydroxyl group directed *syn*-addition/*syn*-elimination appears unlikely. Alternatively, Maseras has provided computational evidence for an *anti*-addition/*anti*-elimination sequence for the gold(I)-catalyzed isomerization of allylic ethers in the presence of alcohol.<sup>28</sup> A key component of this pathway was the formation of a six-membered chelate structure involving hydrogen bonding between the nucleophile and allylic alkoxy group that both facilitates nucleophilic addition and stabilizes the initially formed cationic intermediate.<sup>29</sup>

Guided by the hypotheses of Maseras, we propose a mechanism involving *anti*-addition/*anti*-elimination to account for the gold(I)-catalyzed conversion of (*R,Z*)-**12** to (*R,E*)-**13**. Within this construct, two diastereomeric reaction manifolds are feasible resulting from cyclization of the diastereomeric gold(I)  $\pi$ -alkene complexes *si-I* and *re-I* (Scheme 2). In the former manifold, outer-sphere addition of the pendant amine to the complexed C=C bond of *si-I* would form the cyclic, hydrogen-bonded gold alkyl intermediate (*R,S,R*)-**II**. Proton transfer to the hydroxyl group followed by *anti*-elimination of water and displacement of gold would form (*R,E*)-**13**. In the latter reaction manifold, outer-sphere addition of the pendant amine to the complexed C=C bond of *re-I* to form (*S,R,R*)-**II** followed by proton transfer, *anti*-elimination, and alkene displacement would form (*S,Z*)-**13** (Scheme 2). A rationale for selective formation of (*R,E*)-**13** in preference to (*S,Z*)-**13** can be found in the consideration of the potential chairlike conformations of the initially formed hydrogen-bonded bicyclic structures (*R,S,R*)-**II** and (*S,R,R*)-**II**. Whereas intermediate (*R,S,R*)-**II** can adopt a fully equatorial-substituted *cis*-decalin type conformation, intermediate (*S,R,R*)-**II** possesses a pseudoaxial methyl substituent. This latter

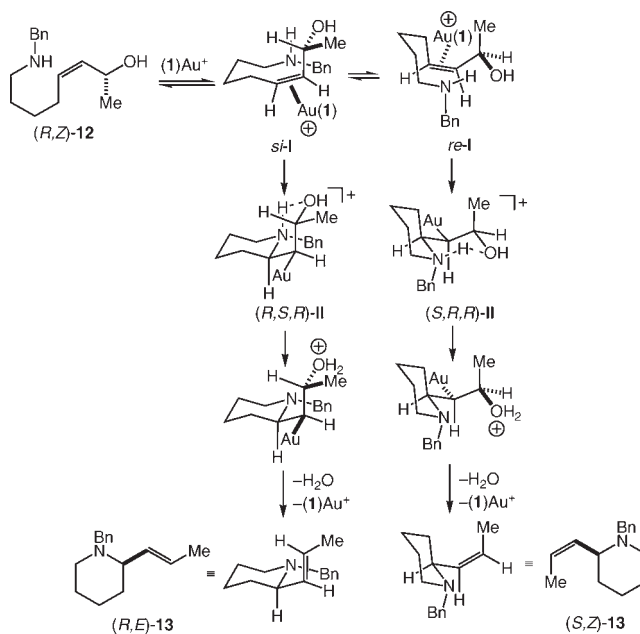
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Scheme 2



species should experience unfavorable 1,3-diaxial interaction with the piperidine methylene group, thereby disfavoring cyclization of gold  $\pi$ -alkene complex *re-I* leading to selective formation of (*R,E*)-**13**.

In summary, we have developed a gold(I)-catalyzed protocol for the intramolecular amination of allylic alcohols with secondary alkylamines. The procedure tolerated a number of alkylamines and substitution patterns, was effective for the synthesis of both pyrrolidine and piperidine derivatives, and occurred with selective 1,3-chirality transfer in the conversion of (*R,Z*)-**12** to (*R,E*)-**13**. This latter observation established the net *syn* addition of the amine relative to the departing hydroxyl group.

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**Supporting Information Available.** Experimental procedures, analytical and spectroscopic data, and copies of HPLC traces and NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.