Allylic Amination

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

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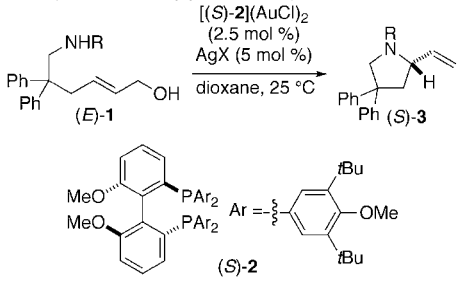
The transition-metal-catalyzed enantioselective amination of allylic esters and carbonates represents one of the most well-established routes to chiral, nonracemic allylic amines.[1] With the potential to condense synthetic sequences and reduce waste streams, the dehydrative amination of allylic alcohols as a route to enantiomerically enriched allylic amines has gained considerable interest. However, while the stereospecific amination of chiral secondary allylic alcohols has been demonstrated,[2–4] the enantioselective amination of allylic alcohols remains problematic.[5] Carreira et al. have reported the Ir^{I}-catalyzed enantioselective amination of 1-cyclohexyl-prop-2-enol with sulfamic acid in 70% *ee*.[6] Hartwig et al. have reported the Ir^{I}/BPh_3-catalyzed enantioselective intermolecular amination of primary 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.[7] The groups of Yamamoto[8] and Kitamura[9] 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. Herein 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.[4,10] Encouraged by the high efficiency and stereospecificity of this transformation and guided by both our previous work in the area of gold(I)-catalyzed enantioselective allene hydroamination[11,12] and Bandini's recent demonstration of gold(I)-catalyzed enantioselective arylation[13] and alkoxylation[14] of allylic alcohols,[15] we targeted axially chiral bis(gold) complexes as catalysts for the intramolecular enantioselective amination of the ε-benzylamino allylic alcohol (*E*)-**1a** (Table 1). Unfortunately, optimization within this framework[16] proved largely unsuccessful: treatment of (*E*)-**1a** with a catalytic 1:2 mixture of [(*S*)-**2**]$(AuCl)_2$ and $AgSbF_6$ 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).[17] We then focused our attention on the manipulation of the nitrogen nucleophile as a means to amplify stereoinduction (Table 1). These experiments proved fruitful and gold(I)-catalyzed cyclization of Fmoc-protected ε-amino allylic alcohol (*E*)-**1g** employing an optimized catalyst system comprised of [(*S*)-**2**]$(AuCl)_2$ (2.5 mol%) and $AgClO_4$ (5 mol%) in dioxane at room temperature for 48 h led to the isolation of (*S*)-**3g** in 95% yield with 91% *ee* (Table 1, entry 7).[16,18]

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



Entry	**1** + **3**, R[a]	X	Time [h]	Yield [%][b]	*ee* [%][c]
1	**a**, Bn	SbF_6	5	100[d]	29
2	**b**, Cbz	ClO_4	48	99	79
3	**c**, Boc	ClO_4	48	97	80
4[e]	**d**, Troc	ClO_4	48	62	84
5	**e**, CO_2Me	ClO_4	48	97	75
6	**f**, Ts	ClO_4	48	98	76
7	**g**, Fmoc	ClO_4	48	95	91

[a] Bn = benzyl, Cbz = benzyloxycarbonyl, Boc = *tert*-butyloxycarbonyl, Troc = 2,2,2-trichloroethoxycarbonyl, Ts = 4-toluenesulfonyl, Fmoc = fluorenylmethyloxycarbonyl. [b] Yield of isolated product. [c] Determined by HPLC analysis on chiral support. [d] Conversion. [e] Reaction run at 40 °C.

The scope of this gold(I)-catalyzed enantioselective intramolecular amination was evaluated as a function of alkene configuration, substitution, and ring size (Table 2). The enantioselectivity of the amination was sensitive to the alkene configuration: (*Z*)-**1g** was converted into **3g** in 99% yield with ≤5% *ee* (Table 2, entry 1). Although ε-amino allylic alcohols that possessed *gem*-dialkyl substitution at the homoallylic position cyclized with higher enantioselectivity than did an unsubstituted ε-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 a 1:1 mixture of

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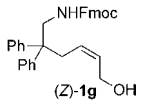
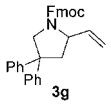
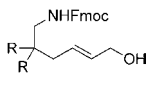
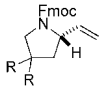
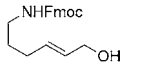
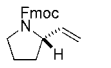
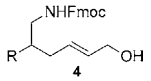
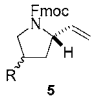
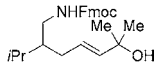
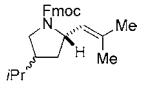
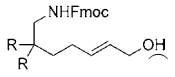
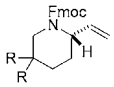
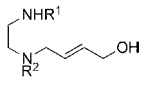
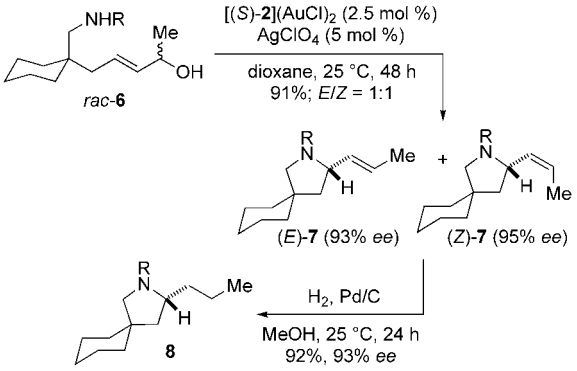
Table 2: Substrate scope of the intramolecular amination of allylic alcohols (0.6 M) catalyzed by a 1:2 mixture of [(*S*)-**2**](AuCl)$_2$ (2.5 mol%) and $AgClO_4$ (5 mol%) in dioxane at 25 °C for 48 h.[18]

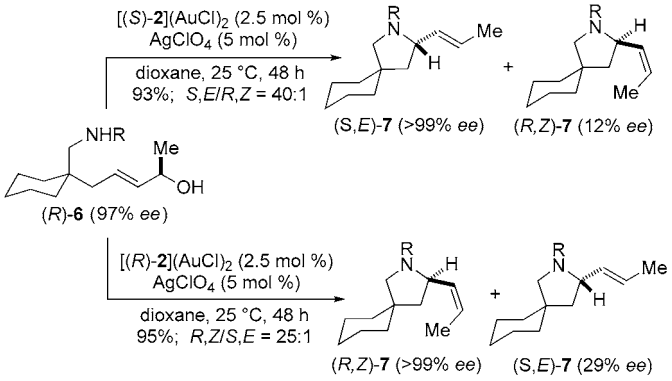
Entry	Substrate	Heterocycle	Yield [%][a]	*ee* [%][b]
1	 (*Z*)-**1g**	 **3g**	99	≤5
2	 R = Me		94	90
3	RR = $(CH_2)_5$		95	94
4			89	62
5	 **4** R = Ph[c]	 **5**	87[d]	90/92
6	R = *i*Pr		98[d]	85/91
7			87[d]	88/90
8	 RR = $(CH_2)_5$		69	77
9[c]	 R^1 = Fmoc, R^2 = Boc		86	94
10[c]	R^1 = Fmoc, R^2 = Ts		99	92
11[e]	R^1 = Boc, R^2 = Fmoc		99	91

[a] Yield of isolated product. [b] Determined by HPLC analysis on chiral support. [c] Compounds **4** and **5**: R = Ph (entry 5). [d] Diastereomeric ratio ≈ 1:1. [e] Reaction run at 50 °C.



Scheme 1. Cyclization of *rac*-**6** catalyzed by [(*S*)-**2**](AuCl)$_2$/$AgClO_4$. R = Fmoc.

possessed the same absolute configuration (*S* by analogy),[18] 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 (Scheme 2), cyclization of enantiomerically enriched (*R*)-**6** catalyzed by [(*S*)-**2**]-(AuCl)$_2$/$AgClO_4$ led to isolation of a 40:1 mixture of (*S*,*E*)-**7** and (*R*,*Z*)-**7** in 93% combined yield while cyclization of (*R*)-**6** catalyzed by [(*R*)-**2**](AuCl)$_2$/$AgClO_4$ led to isolation of a 25:1

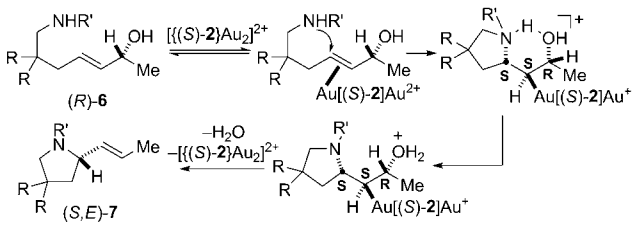


Scheme 2. Cyclization of enantiomerically enriched (*R*)-**6** (97% *ee*) catalyzed by [(*S*)-**2**](AuCl)$_2$/$AgClO_4$ (top pathway) and [(*R*)-**2**](AuCl)$_2$/$AgClO_4$ (bottom pathway). R = Fmoc.

cis and *trans* diastereomers, both of which were formed with ≥90% *ee*, indicative of overriding catalyst control of stereoinduction. The gold-catalyzed enantioselective amination also tolerated *gem*-dialkyl substitution at the hydroxy-bound carbon atom (Table 2, entry 7) and was applicable to the synthesis of six-membered nitrogen heterocycles (Table 2, entries 8–11), proving particularly effective for the synthesis of differently protected 2-vinylpiperazines (Table 2, entries 9–11).

The effect of a chiral secondary allylic alcohol moiety on the efficiency and stereoselectivity of this gold-catalyzed allylic amination was evaluated employing ε-amino allylic alcohol **6**. In one experiment (Scheme 1), cyclization of *rac*-**6** catalyzed by [(*S*)-**2**](AuCl)$_2$/$AgClO_4$ led to isolation of a 1:1 mixture of (*E*)-**7** and (*Z*)-**7** in 91% combined yield. Hydrogenation of this mixture formed 2-propylpyrrolidine **8** in 92% yield with 93% *ee*, which established that (*E*)-**7** and (*Z*)-**7** mixture of (*R*,*Z*)-**7** and (*S*,*E*)-**7** in 95% combined yield. Together, these results established that asymmetric induction is determined solely by the 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 hydroxy group by the attacking carbamate nucleophile.

The net *syn* displacement of the hydroxy group by the nitrogen nucleophile, which was also documented for the amination of allylic alcohols catalyzed by achiral mono(gold) complexes,[3,4] is consistent with a mechanism involving π-complexation of gold to the C=C bond followed by *anti*-addition of the nucleophile and *anti*-elimination of the hydroxy group, perhaps facilitated by an intramolecular N–H–O hydrogen bond (Scheme 3).[19] Alternatively, *syn*-sub-



Scheme 3. Proposed mechanism of the gold-catalyzed allylic amination of (*R*)-**6**. RR = $(CH_2)_5$, R′ = Fmoc.

stitution is also consistent with a mechanism involving σ-activation of the hydroxy group followed by concerted S_N2' displacement[20] and Toste et al. have recently demonstrated that bis(gold) phosphine complexes are sufficiently Lewis acidic to acidify the hydroxy proton of an alcohol.[21] However, the failure of either triflic acid or $BF_3{\cdot}OEt_2$ (10 mol%, 25 °C, 48 h) to catalyze the cyclization of (*E*)-**1g** argues against a σ-activation pathway for this 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 ε-amino allylic alcohols that possessed a stereogenic homoallylic or hydroxy-bound carbon atom occurred with overriding catalyst control of asymmetric induction. Stereochemical analysis of the cyclization of (*R*)-**6**, which possessed a secondary allylic alcohol moiety, established the net *syn*-displacement of the hydroxy group by the carbamate nucleophile.

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[16] A full description of the optimization studies is provided in the Supporting Information.

[17] Using a 1:1 mixture of [(*S*)-**2**]$(AuCl)_2$ and $AgSbF_6$ led to significant decrease in both rate and enantioselectivity.[16]

[18] The absolute configuration of (*S*)-**3b** was determined by comparison to the HPLC trace of (*R*)-**3b**.[11a] 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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