

Gold(I)-Catalyzed Highly Regio- and Stereoselective Decarboxylative Amination of Allylic *N*-Tosylcarbamates via Base-Induced Aza-Claisen Rearrangement in Water

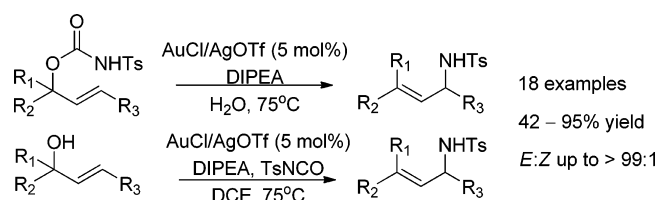
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ABSTRACT



A gold(I)-catalyzed decarboxylative amination of allylic *N*-tosylcarbamates via base-induced aza-Claisen rearrangement has been developed. A variety of substituted *N*-tosyl allylic amines were obtained in good yield, excellent regioselectivity, and high to excellent stereoselectivity. This transformation could be performed either in H₂O or in one pot directly from allylic alcohols and therefore represents an efficient and environmentally benign protocol for the synthesis of *N*-tosyl allylic amines.

Allylic amines are important and versatile synthetic intermediates in organic synthesis.¹ Aza-Claisen rearrangement of allylic imidates (Overman rearrangement) represents a highly efficient and attractive method for the synthesis of allylic amines because of its excellent regio- and stereocontrol through the highly ordered chairlike transition state.² In the past few decades, transition metal catalysis has been introduced to this classical transformation, enabling it to be performed under very mild conditions³ and even providing asymmetric induction with the use of chiral ligands.⁴ Despite

a wide choice of soft metal catalysts available for the [3,3]-sigmatropic rearrangement,⁵ Pd(II) and Hg(II) salts are the only catalysts that have been successfully applied to the aza-Claisen rearrangement. Therefore, simple and efficient metal catalysts are still highly desirable for this transformation.

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Homogeneous gold catalysis has found wide applications in organic synthesis.⁶ As soft and carbophilic Lewis acids, they can coordinate and activate unsaturated C–C bonds toward intramolecular nucleophilic attack. On the basis of this catalytic mode, gold-catalyzed [3,3]-sigmatropic rearrangement of propargylic esters to allenyl esters⁷ and allenyl carbinol esters to 1,3-butadien-2-ol esters⁸ and the isomerization of allylic acetates⁹ have been well studied. AuCl and AuCl₃ have also been used to catalyze aza-Claisen rearrangement of allylic trichloroacetimidates; however, only limited substrate scope (i.e., C1-substituted substrates) and poor to moderate yields were obtained.¹⁰ Herein we report a highly efficient gold(I)-catalyzed, base-induced decarboxylative aza-Claisen rearrangement of allylic *N*-tosylcarbamates. This transformation provides a highly regio- and stereoselective method for the preparation of *N*-tosyl allylic amines from readily available allylic alcohols instead of allenes or 1,3-dienes as reported in the literature.¹¹

N-Substituted allylic carbamates are generally used for the synthesis of allylic amines via low-valent transition metal catalyzed decarboxylative allylic substitution.¹² They are also good candidates for decarboxylative aza-Claisen rearrangement once the NH group is deprotonated with a base. Such transformation has been achieved thermally in which allylic *N*-phenylcarbamates were treated with NaH at elevated temperatures to give *N*-phenyl allylic amines.¹³ However, very few metal catalysts have been introduced to this kind of transformation.¹⁴ We chose allylic *N*-tosylcarbamates as the starting point because it is highly acidic ($pK_a = 8.5$) and can be completely deprotonated with simple organic base. With 1 equiv of diisopropylethylamine (DIPEA) and **1a** in toluene, a series of gold catalysts were examined. The best result was obtained when 5 mol % AuCl/AgOTf was used, affording **2a** in 60% yield (Table 1, entries 1–6). Solvent screening revealed that 1,2-dichloroethane (DCE) was the best choice, leading to 90%

isolated yield of **2a** within 3 h (Table 1, entry 7).¹⁵ Remarkably, we discovered that the reaction run in water was as efficient as that in DCE (Table 1, entry 8).

Control experiments revealed that both the Au(I) catalyst and base are necessary for this transformation. In the presence of DIPEA, the reaction did not proceed in water without AuCl/AgOTf or with AgOTf alone, even at 100 °C for 12 h. In contrast, in the absence of the base, complete decomposition of **1a** to *p*-toluenesulfonamide took place under the AuCl/AgOTf catalysis condition in less than 3 h.¹⁶ By screening various organic and inorganic bases,¹⁵ we found that a complete deprotonation of **1a** with a stoichiometric amount of DIPEA was essential to prevent the undesired decomposition and therefore ensure a high yield of **2a**. Other *N*-substituted allylic carbamates such as *N*-Cbz- and *N*-Boc-substituted substrates were also investigated under the optimized conditions; however, no corresponding allylic amines were produced. These results indicated that the reactivity of the substrate is highly dependent on the NH acidity of the carbamate.

With optimized conditions in hand, we further tested the substrate scope of this decarboxylative allylic amination in water. Monosubstituted olefinic substrates generally gave the desired products in good yields (Table 2, entries 1–5). When the allylic position (C3) was substituted with alkyl or aryl groups, high stereoselectivities (88:12 to 97:3) were achieved with *E* isomers as the main products (Table 2, entries 2–4, 6, and 11). Conjugated *N*-tosyl dienylamine **2g** was produced from the 1,4-diene substrate **1g** in a moderate yield with a 88:12 *E/Z* ratio (Table 2, entry 6). 1,2-Disubstituted olefinic substrates were also examined, and the steric effect seemed to be crucial. For substrates with less hindered substituent at C1 position, the corresponding products were obtained in good yields (Table 2, entries 7 and 8), whereas only moderate yields for more hindered *sec*-butyl- or benzyl-substituted substrates, even after prolonged reaction time (Table 2, entries 9 and 10). Cyclohex-2-enyl *N*-tosylcarbamate (**1m**) also afforded the desired product **2m** in a 42% yield (Table 2, entry 12).

Table 1. Optimization of Reaction Conditions^a

entry	catalyst	solvent	time (h)	conv (%) ^{b,c}
1	AuCl	toluene	3	10
2	AuCl/AgOTf	toluene	3	62 (60)
3 ^d	Au(L ₁)Cl/AgOTf	toluene	3	<5
4 ^d	Au(L ₂)Cl/AgOTf	toluene	3	<5
5	AuCl ₃	toluene	3	12
6	AuCl ₃ /AgOTf	toluene	3	10
7	AuCl/AgOTf	DCE	3	92 (90)
8	AuCl/AgOTf	H ₂ O	3	90 (89)
9 ^e		H ₂ O	12	0
10 ^e	AgOTf	H ₂ O	12	0
11 ^f	AuCl/AgOTf	H ₂ O	3	decomp

^a Reaction condition: 0.3 mmol substrate in the indicated solvent.

^b Conversion determined by ¹H NMR with nitrobenzene as internal standard. ^c Isolated yields shown in the parentheses. ^d L₁ = PPh₃, L₂ = [P(*t*-Bu)₂](*o*-Phenyl)Ph]. ^e At 100 °C. ^f Without DIPEA.

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Table 2. Decarboxylative Amination of Allylic *N*-Tosylcarbamates in H₂O^a

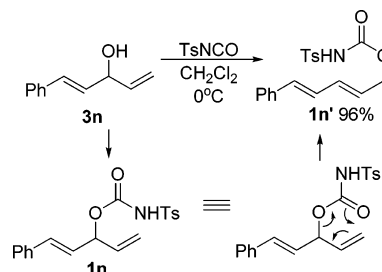
entry	substrate	product	time (h)	yield (%) ^{b, c}
1			1	95
2			2	90 <i>E</i> : <i>Z</i> , 97/3
3			2	90 <i>E</i> : <i>Z</i> , 95/5
4			2	92 <i>E</i> : <i>Z</i> , 96/4
5			2	93
6			12	61 <i>E</i> : <i>Z</i> , 88/12
7			3	92
8			3	84
9 ^d			24	78
10 ^d			24	69
11			2	94 <i>E</i> : <i>Z</i> , 90/10
12 ^d			24	42

^a Unless otherwise indicated, all reactions were carried out on a 0.3 mmol scale with 5 mol % AuCl/AgOTf and 1 equiv of DIPEA in H₂O for the indicated time. ^b Isolated yield. ^c *E*/*Z* ratio determined by ¹H NMR. ^d At 100 °C.

Considering the potential importance of conjugated dienyamines in the synthesis of complex nitrogen-containing natural products,¹⁷ we decided to further expand the substrate scope to C3-alkenyl-substituted substrates. However, when C3-alkenyl-substituted allylic alcohol **3n** was subjected to tosyl isocyanate (TsNCO) in CH₂Cl₂, the C1-alkenyl-substituted product **1n'**, instead of the desired product **1n**, was produced exclusively even at 0 °C. We proposed that a rapid [3,3]-sigmatropic oxo-rearrangement occurs once the C3-alkenyl-

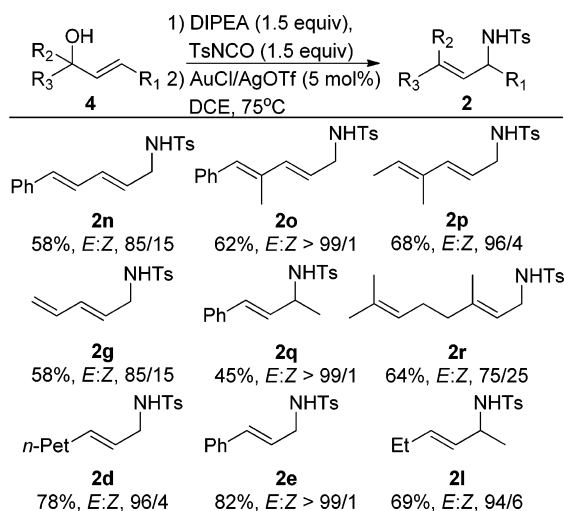
substituted carbamate **1n** is generated. Here the driving force is to form the more stable product **1n'** with a conjugated diene unit (Scheme 1). Similar oxo-rearrangement was also observed

Scheme 1. Unexpected [3,3]-Oxo-Rearrangement



for substrates **1e**, **1f**, and **1g** after their storage at room temperature for several days. However, those substrates underwent the Au(I)-catalyzed decarboxylative amination without oxo-rearrangement at high temperature (75 °C) in the presence of DIPEA. This revealed the importance of DIPEA in preventing the undesired oxo-rearrangement, probably by converting the substrates into their imidate form. Thus, we modified the procedure by adding DIPEA to a solution of **3n** in DCE prior to the addition of TsNCO. AuCl and AgOTf were then added directly to the above mixture, and the temperature was raised to 75 °C. To our delight, the desired conjugated dienyamine **2n** was produced as the only rearrangement product in a 58% overall yield with a 85:15 *E*/*Z* ratio after 3 h. This one-pot synthesis not only efficiently prevents the undesired oxo-rearrangement but also avoids additional isolation and purification steps. By following this one-pot procedure, a series of conjugated *N*-tosyl dienyamines (Scheme 2, **2n–p** and **2g**)

Scheme 2. Products Obtained via One-Pot Synthesis^{a,b,c}

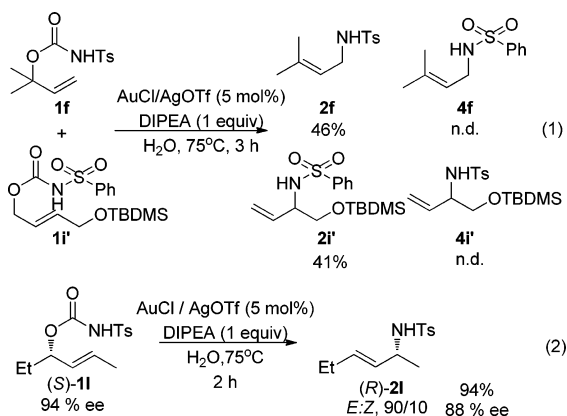


^a Reaction conditions: to **4** (0.5 mmol) and DIPEA (1.5 equiv) in DCE (5 mL) was added TsNCO (1.5 equiv), then 5 mol % AuCl/AgOTf was added and the temperature was raised to 75 °C for 3 h. ^b Isolated yield. ^c *E*/*Z* ratio determined by ¹H NMR.

were prepared from C3-substituted allylic alcohols in moderate yield with good to excellent stereoselectivity. Several C3-substituted and C1,C3-disubstituted substrates were also tested (Scheme 2). Compared with the two-step procedure, the one-pot protocol afforded even higher stereoselectivity for substrates **2d**, **2e**, and **2l**.

To probe the reaction mechanism, a crossover experiment was conducted under standard condition with a 1:1 mixture of **1f** and **1i'** (Scheme 3, eq 1). The crossover products **4f**

Scheme 3. Crossover Experiment and Chirality Transfer



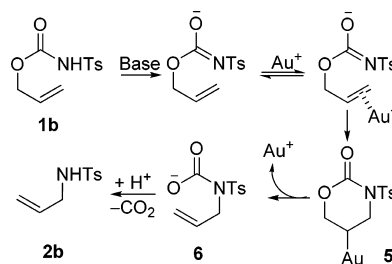
and **4i'** were not detected at all by either LC-MS or ^1H NMR, whereas the concerted products **2f** and **2i'** were obtained in 46% and 41% isolated yield, respectively. This result strongly suggests the involvement of a concerted mechanism. When the enantiopure substrate (*S*)-**11** was employed, (*R*)-**21** was obtained with an almost complete chirality transfer (Scheme 3, eq 2). This result further proved the concerted mechanism and provided an efficient way to prepare chiral allylic amines starting from readily available enantiopure allylic alcohols.

On the basis of these results, we propose a cyclization-induced aza-Claisen rearrangement pathway to account for

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the product formation (Scheme 4). First, DIPEA deprotonates the *N*-tosylcarbamate into its imidate form, and then the

Scheme 4. A Plausible Mechanism



nitrogen of the imidate undergoes intramolecular nucleophilic attack on the Au(I)-activated double bond, leading to the six-membered-ring intermediate **5**. Grob-type fragmentation regenerates the Au^+ catalyst along with the rearranged allylic *N*-tosylcarbamate ion **6**, which subsequently undergoes decarboxylation and protonation to give the *N*-tosyl allylic amine product.

In conclusion, we have developed an efficient gold(I)-catalyzed decarboxylative amination of allylic *N*-tosylcarbamates via base-induced aza-Claisen rearrangement. A variety of substituted *N*-tosyl allylic amines were obtained in good yield, excellent regioselectivity, and high to excellent stereoselectivity. This transformation could be performed either in H_2O or in one pot directly from allylic alcohols and therefore represents an efficient and environmentally benign protocol for the synthesis of *N*-tosyl allylic amines.

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Supporting Information Available: Experimental procedures and spectral data for **1** and **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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