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Gold-Catalyzed Tandem Cycloisomerization and Dimerization of Chiral Homopropargyl Sulfonamides

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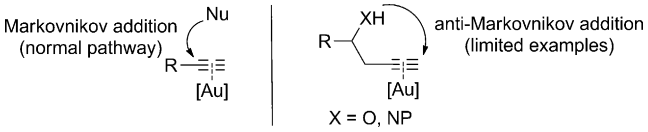
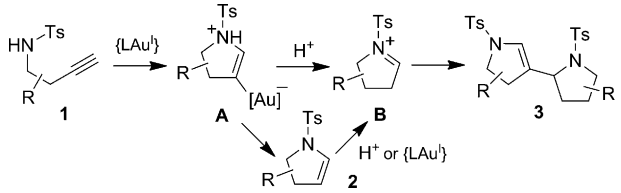
In the past decade, gold-catalyzed addition of a heteroatom nucleophile to a C–C multiple bond, in most cases an alkyne, has proven to be a powerful tool in organic synthesis,[1] providing easy access to an incredible variety of different cyclic compounds, especially the heterocyclic motifs.[2] It is surprising, however, that few examples have been reported of gold-catalyzed 5-*endo*-dig cyclization of terminal alkyne.[3] A likely reason for this paucity is that this gold-catalyzed cycloisomerization reaction[4] involves an anti-Markovnikov addition, while Markovnikov regioselectivity was normally observed for gold-catalyzed nucleophilic addition to terminal alkynes (Scheme 1).[5]



Scheme 1. Gold-catalyzed nucleophilic addition to a terminal alkyne.

In our recent study toward such a gold-catalyzed 5-*endo*-dig cyclization of terminal alkynes, we reported a gold-catalyzed tandem cycloisomerization/oxidation of homopropargyl alcohol for the synthesis of synthetically useful γ-lactones.[6] On the basis of this reaction, we developed a similar gold-catalyzed oxidative cyclization of chiral homopropargyl sulfonamides, leading to the enantioenriched γ-lactam products.[7] Inspired by these results, we envisioned taking advantage of intermediate **A**, which could be further transformed into the enamide intermediate **2** and iminium intermediate **B** in the presence of acid. Finally, the enamide **2**[8] would attack the iminium intermediate **B** to lead to the formation of dimer **3** (Scheme 2).[9] Herein, we describe the realization of such a Au-catalyzed dimerization, which has been long neglected in the area of Au-catalyzed cycloisomerization, affording enantioenriched pyrrolidines in generally good to excellent yields. Mechanistic studies revealed that the reaction presumably proceeds through a gold-catalyzed 5-*endo*-dig cyclization and subsequent dimerization catalyzed both by gold and methanesulfonic acid (MsOH).



Scheme 2. Initial reaction design. Ts = toluene-4-sulfonyl.

We set out to screen different conditions for this reaction by using chiral homopropargyl sulfonamide **1a** as the model substrate. To our delight, in the presence of 5 mol% [PPh_3AuNTf_2] and 1.0 equiv of MsOH, the tandem reaction proceeded well to give the corresponding dimerization product **3a** in 64% yield, as determined by ^1H NMR spectroscopy (Table 1, entry 1). Then, the effect of acid was investigated, and it was found that the use of other acid failed to improve the yield (Table 1, entries 1–3). Gratifyingly, the yield could be further improved to 70% in the presence of 0.5 equiv MsOH (Table 1, entry 4). The reaction also worked in the absence of acid, albeit in diminished yield and with longer reaction time (Table 1, entry 5). Among the different gold catalysts screened (Table 1, entries 7–14), [$IPrAuNTf_2$] was found to be the best one, and 92% yield could be achieved (Table 1, entry 10). In the absence of acid, only 65% yield was obtained even by employing [$IPrAuNTf_2$] as the gold catalyst (Table 1, entry 15). Without using any gold catalyst, no **3a** formation was observed under the acidic reaction conditions, and $AgNTf_2$ was not effective in promoting this reaction (Table 1, entry 17). Notably, $PtCl_2$ could also catalyze this reaction, but with low efficiency even at 80 °C (Table 1, entry 16).

Under the optimal reaction conditions, various chiral homopropargyl sulfonamides **1**, easily prepared by using Ellman's *tert*-butylsulfinimine chemistry,[7,10] were tested to examine the generality of the current reaction. As shown in Table 2, except for the substrate **1p**, which only gave 53% yield (Table 2, entry 16), good to excellent yields could be achieved in all cases, and no dihydropyrrole products **2** were observed. In addition, the reaction was generally tolerant of

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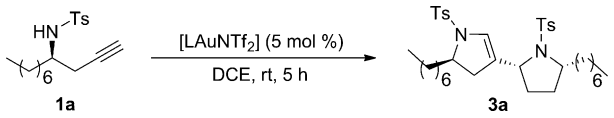
Table 1. Optimization of reaction conditions.[a]



1a 3a

Entry	Gold catalyst	Acid [equiv]	Yield [%][b]
1	$[Ph_3PAuNTf_2]$	MsOH (1.0)	64
2	$[Ph_3PAuNTf_2]$	CF_3CO_2H (1.0)	59
3	$[Ph_3PAuNTf_2]$	$HNTf_2$ (1.0)	<5
4	$[Ph_3PAuNTf_2]$	MsOH (0.5)	70
5[c]	$[Ph_3PAuNTf_2]$	–	57
6	$[Ph_3PAuNTf_2]$	MsOH (1.5)	53
7	[Cy-JohnPhosAuNTf$_2$]	MsOH (0.5)	62
8	[XPhosAuNTf$_2$]	MsOH (0.5)	75
9	[BrettPhosAuNTf$_2$]	MsOH (0.5)	78
10	[IPrAuNTf$_2$]	MsOH (0.5)	92
11	$[Et_3PAuNTf_2]$	MsOH (0.5)	65
12	$[(4\text{-}CF_3C_6H_4)_3PAuNTf_2]$	MsOH (0.5)	68
13	$[(C_6F_5)_3PAuNTf_2]$	MsOH (0.5)	43
14	Au^{III}[d]	MsOH (0.5)	<5[e]
15[c]	[IPrAuNTf$_2$]	–	65
16[f]	$PtCl_2$	MsOH (0.5)	36
17	$AgNTf_2$	MsOH (0.5)	<5

[a] Reaction conditions: [**1a**] = 0.10 M; DCE = 1, 2-dichloroethane, Tf = SO_2CF_3, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [b] Estimated by ^{1}H NMR spectroscopy using diethyl phthalate as internal reference. [c] Time = 8 h. [d] Dichloro(2-picolinato)gold(III). [e] 90% of **1a** remained unreacted. [f] Toluene, 80 °C.

various functional groups, including a remote benzyl ether (OBn) group (Table 2, entry 6), *N*-phthaloyl (Table 2, entry 5), and an azido group (Table 2, entry 4). Importantly, the compounds **3a**–**n** were formed with excellent diastereoselectivities (>50:1, determined by ^{1}H NMR spectroscopy of the crude reaction mixtures) and, according to the X-ray analysis of **3i** (Figure 1), the same stereochemical outcome was assumed for all the pyrrolidines synthesized. It should be mentioned that in these transformations, the *ee* values could be well maintained, as we determined the *ee* values of the compound **3c** as a representative example (Table 2, entry 3).

Although *N*-homopropargyl carboxamides are not suitable substrates due to the competing gold-catalyzed amide 6-*exo*-dig cyclization,[11] we were pleased to find that the reaction could also proceed well for Ns and Bus protected substrates **1q** and **1r**, resulting in high yields of the desired products **3q** and **3r** (88% and 82% yields of isolated product) with excellent diastereomeric ratios (>50:1). Notably, both reactions were initially met with poor yields in the previously optimized reaction conditions; however, simply switching the gold catalyst from [IPrAuNTf$_2$] to [BrettPhosAuNTf$_2$] resulted in a significant improvement of the yields (Scheme 3).

To probe the reaction mechanism, we first prepared the dihydropyrrole substrate **2a**[12] to investigate the reaction. As shown in the reaction in Table 3, dihydropyrrole **2a** could dimerize in the presence of 5 mol% gold catalyst to afford the corresponding **3a** in 53% yield as determined by ^{1}H NMR spectroscopy (Table 3, entry 1). Interestingly, by

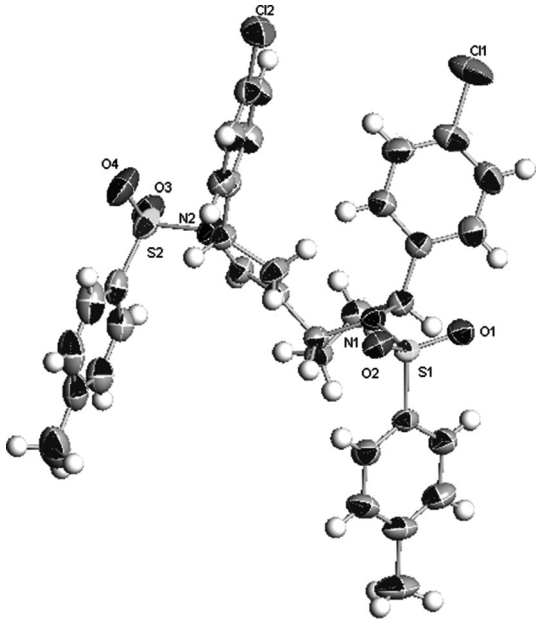
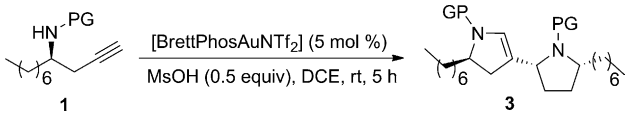


Figure 1. Crystal structure of compound **3i**. Thermal ellipsoids are set at the 30% probability level.



1 3

1q: PG = Ns **3q**: 88% yield

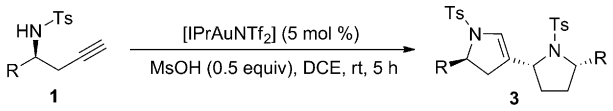
1r: PG = Bus **3r**: 82% yield

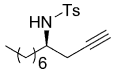
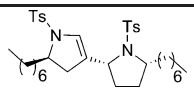
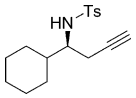
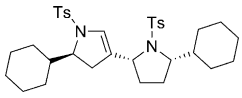
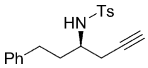
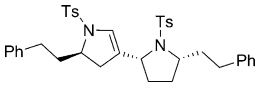
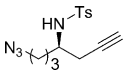
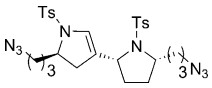
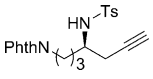
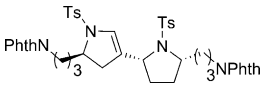
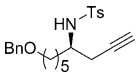
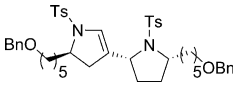
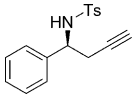
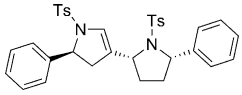
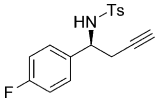
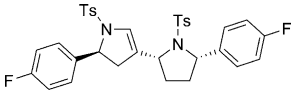
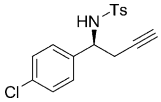
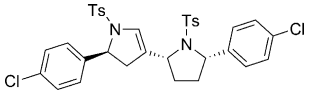
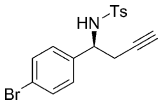
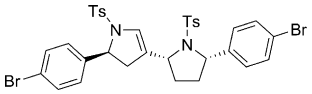
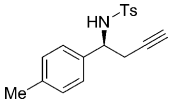
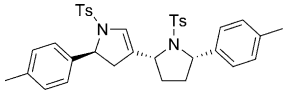
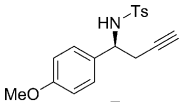
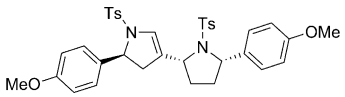
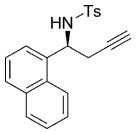
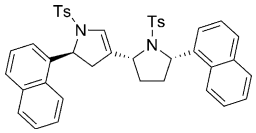
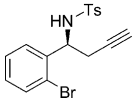
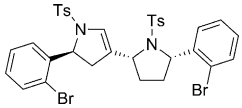
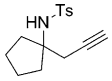
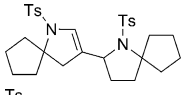
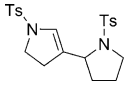
Scheme 3. Gold-catalyzed tandem cycloisomerization/dimerization of chiral homopropargyl amides **1q** and **1r**. Bus = *tert*-butylsulfonyl, Ns = 2-nitrobenzenesulfonyl.

employing 0.5 equivalents MsOH as the catalyst, **2a** could also be readily converted into **3a** in 64% yield (Table 3, entry 2). Moreover, treatment of **2a** with a combination of 5 mol% gold and 0.5 equivalents MsOH produced the corresponding **3a** in 78% yield (Table 3, entry 3). These results clearly suggested that the dimerization process could be catalyzed both by gold and protic acid, which allowed the rapid isomerization of enamide into reactive iminium species and eventually led to the formation of dimer. This finding is quite consistent with the known acid-catalyzed dimerization of enamide.[9]

In addition, we also monitored the tandem reaction by ^{1}H NMR spectroscopy, as detailed in Figure 2. In this case, the reaction was performed in the absence of MsOH in order to better track the reaction intermediates. At the early stage of the reaction, we could clearly observe the formation of the dihydropyrrole **2a** and the 2-hydroxypyrrolidine intermediate **4a**,[13] which were gradually transformed into the final dimer **3a**. These observations strongly support our initial hypothesis that the reaction involves the formation of enamide **2**.

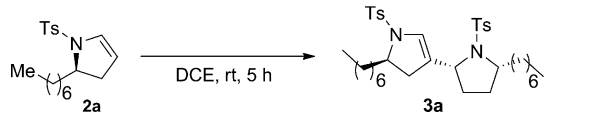
Table 2. Reaction scope study.[a]



Entry	Substrate	1	Product	3	Yield [%]
1		**1a**		**3a**	85
2		**1b**		**3b**	84
3		**1c**		**3c**[b]	85
4		**1d**		**3d**	80
5		**1e**		**3e**	75
6		**1f**		**3f**	88
7		**1g**		**3g**	86
8		**1h**		**3h**	86
9		**1i**		**3i**	87
10		**1j**		**3j**	84
11		**1k**		**3k**	90
12		**1l**		**3l**	87
13		**1m**		**3m**	92
14		**1n**		**3n**	85
15		**1o**		**3o**	84
16		**1p**		**3p**	53

[a] Reactions run in vials; [**3**] = 0.10 M; yields of isolated products are reported. [b] 99% *ee*, determined using HPLC on a chiral stationary phase.

Table 3. Reaction of dihydropyrrole.



Entry	Catalyst	Yield [%][a]
1	[IPrAuNTf$_2$] (5 mol%)	53
2	MsOH (0.5 equiv)	64
3	[IPrAuNTf$_2$] (5 mol%), MsOH (0.5 equiv)	78

[a] Determined by ^{1}H NMR spectroscopy.

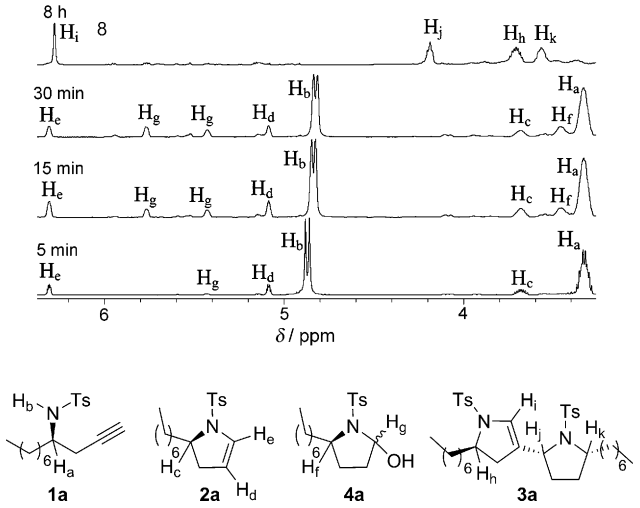
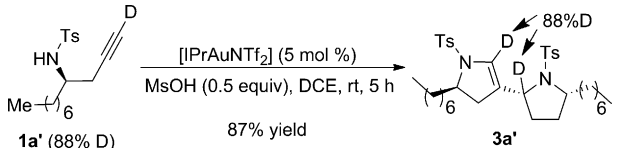
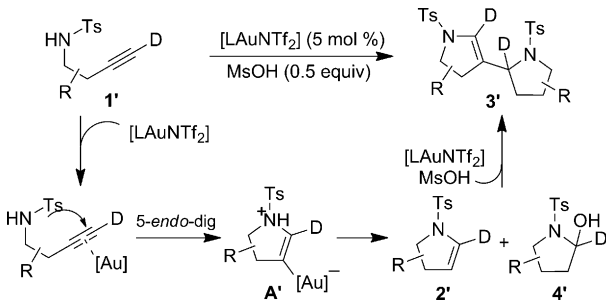


Figure 2. Progression of the tandem reaction as monitored by ^{1}H NMR spectroscopy.

Finally, we performed deuterium labeling studies. It was found that when substrate **1a′** (88% D) was treated under the previously optimized reaction conditions, no deuterium loss was observed [Eq. (1)], which indicates the reaction is presumably triggered by a gold-catalyzed 5-*endo*-dig cyclization of homopropargyl sulfonamide but does not goes through the gold vinylidene intermediate pathway.[14]



On the basis of these experimental observations, a plausible mechanism[15] is proposed for this tandem reaction (Scheme 4). It may initially involve the formation of a π complex through coordination of the gold catalyst to the triple bond of chiral homopropargyl sulfonamide **1′**. A subsequent 5-*endo*-dig cyclization was expected to give the vinyl gold intermediate **A′**, which was transformed into the enamide intermediate **2′** and the 2-hydroxypyrrolidine intermediate **4′**. Finally, both intermediates **2′** and **4′** could be further converted into **3′** catalyzed both by gold and acid. Alternatively, the vinylgold intermediate **A′** might directly



Scheme 4. Plausible catalytic cyclization mechanism.

react with the iminium ion formed by protonation of **2′**, or formed by protonation and elimination of **4′**, to deliver the final dimer.[16]

In conclusion, we have developed a novel gold-catalyzed tandem reaction, which presumably involves gold-catalyzed cycloisomerization/gold- and acid-catalyzed dimerization. Various enantioenriched pyrrolidines can be prepared in generally good to excellent yields with excellent diastereoselectivities from chiral homopropargyl sulfonamides. Other notable features of this method include the use of readily available substrates, the simple procedure, the mild reaction conditions, and in particular, the tolerance of moisture and air (′open flask′). Further related investigations on the gold-catalyzed cycloisomerization-initiated tandem process are under way.

Experimental Section

Typical procedure for gold-catalyzed tandem cycloisomerization/dimerization of chiral homopropargyl sulfonamides

MsOH (2.0 mL, 0.10 M in DCE) and [IPrAuNTf$_2$] (9.0 mg, 0.01 mmol) were added to a solution of the homopropargyl sulfonamides **1** (0.40 mmol) in DCE (2.0 mL) at room temperature. The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC. The reaction typically took 5 h. Upon completion, the reaction was diluted with CH_2Cl_2 (30 mL) and washed with saturated aqueous $NaHCO_3$ (2×15 mL). The resulting solution was extracted again with CH_2Cl_2 (30 mL), and the combined organic layers were dried with $MgSO_4$. The mixture was then concentrated, and the residue was purified by chromatography on silica gel (hexanes/ethyl acetate, 10:1) to afford the desired products **3**.

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Keywords: cycloisomerization · dimerization · domino reactions · gold · homogeneous catalysis

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