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Stereoselective synthesis of 2,5-disubstituted pyrrolidines through gold-catalysed anti-Markovnikov hydroamination-initiated tandem reactions

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A series of gold-catalysed intramolecular anti-Markovnikov hydroamination-initiated azidation, allylation and heteroarylation reactions of chiral homopropargyl sulfonamides have been developed. Various enantioenriched 2,5-disubstituted pyrrolidines are obtained in moderate to excellent yields with excellent enantioselectivities and generally high diastereoselectivities.

Pyrrolidine structural motifs, especially the 2,5-disubstituted pyrrolidines, are present in many bioactive molecules (Figure 1).[1] As a result, a range of synthetic methods have been developed for their synthesis during the past decade.[2] However, successful examples of enantioselective construction of these functionalized pyrrolidines remain scarce.[3] Therefore, the development of novel approach for their preparation is highly desirable.

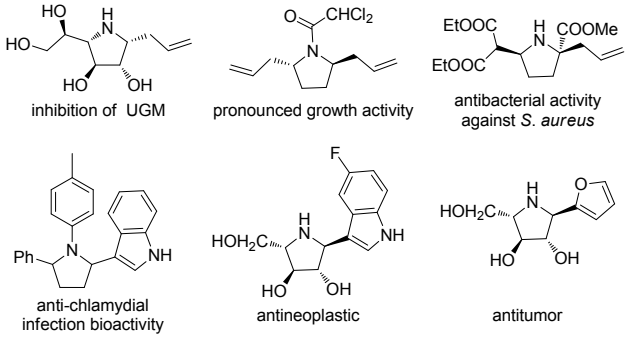
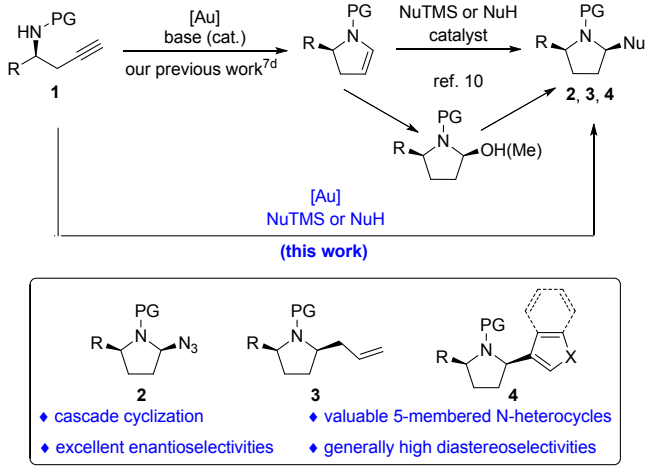


Figure 1 Selected examples of 2,5-disubstituted pyrrolidines in bioactive molecules.

In the past decades, transition-metal-catalysed intramolecular alkyne hydroamination initiated cascade cyclization has proven to be an extremely powerful tool for the straightforward synthesis of various valuable N-heterocycles, but these reactions generally proceed by an *exo*-cyclization pathway via a typical Markovnikov addition in terms of terminal alkynes.[4,5] By utilizing the ring strain strategy[6] to achieve the anti-Markovnikov regioselectivity, our group have developed a variety of gold-catalysed intramolecular alkyne hydroamination initiated oxidation,[7a,b] dimerization,[7c] halogenation,[7e] and hydrogenation,[7f] affording diverse chiral five-membered N-heterocycle skeletons from readily available chiral homopropargyl sulfonamides by a chirality-transfer strategy. However, the external nucleophiles in these cases are still limited to the weak nucleophiles, such as *m*-CPBA,[7a,b] enamide,[7c] water,[7e] and triisopropylsilane.[7f] Inspired by these results and our recent work on the Cu-catalysed cascade cyclization of indolyl homopropargyl amides,[8,9] we envisioned that the stronger nucleophiles such as azidosilanes, allylsilanes and indoles might also trap the iminium intermediates to afford the corresponding 2,5-disubstituted pyrrolidines. Of note, previous synthesis of these pyrrolidines typically starts from the corresponding dihydropyrroles directly or via lactamol intermediates.[10] However, achieving these cascade cyclizations is highly challenging due to the fact that these external strong nucleophiles may also attack the alkyne moiety directly.[11-13]



Scheme 1 Synthesis of enantioenriched 2,5-disubstituted pyrrolidines **2–4** directly from chiral homopropargyl sulfonamides **1**.

Herein, we describe the realization of such a gold-catalysed intramolecular hydroamination-initiated azidation, allylation and heteroarylation, allowing the direct and efficient synthesis of various enantioenriched 2,5-disubstituted pyrrolidines from readily

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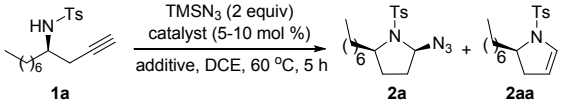
available chiral homopropargyl sulfonamides.[14-16] Importantly, excellent enantioselectivities and generally high diastereoselectivities were achieved in these cascade cyclizations.

At the outset, homopropargyl sulfonamide **1a** was used as the model substrate and $TMSN_3$ (2 equiv) as an extermal nucleophilic reagent for intramolecular hydroamination/azidation reaction. To our delight, by employing 5 mol % of $IPrAuNTf_2$ as catalyst, the tandem reaction proceeded smoothly to produce the desired 2-azido-substituted pyrrolidine **2a** in 47% yield (Table 1, entry 1). Significantly, neither azide–alkyne cycloaddition product[11a,b] nor vinyl azide formation[11d] was observed in this case. Inspired by our previous results that the use of Et_3N as additive might improve the reaction yield,[7d,e] further investigations (Table 1, entries 2–5) revealed that the combination of 1 mol % of Et_3N and 6 mol % of $IPrAuNTf_2$ could lead to the formation of the corresponding pyrrolidine **2a** in 88% yield (Table 1, entry 5). Then, various typical gold catalysts with a range of electronic and steric characteristics were screened, but the yield could not be further improved (Table 1, entries 6–10). Of note, $AgNTf_2$ could also catalyse this reaction to afford the desired product **2a** in 44% yield (Table 1, entry 11) while the use of copper catalysts failed to give even a trace of **2a**.[17]

Table 1 Optimization of reaction conditions[a]

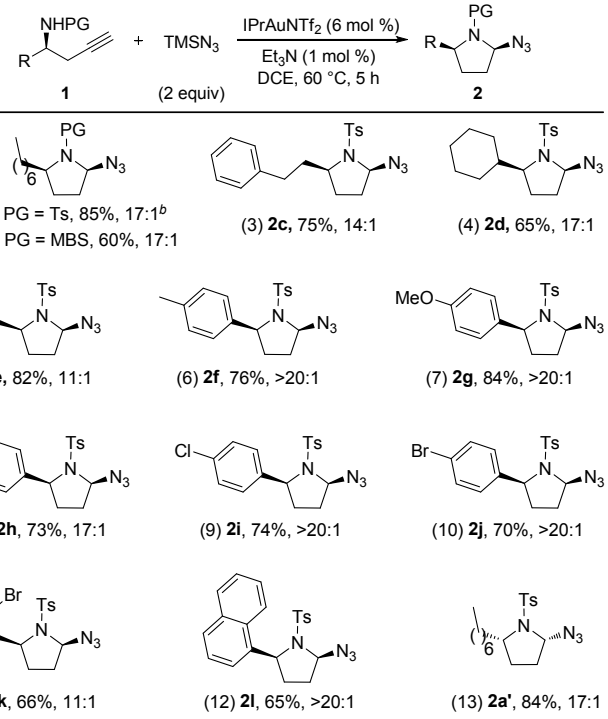


Entry	Catalyst	Additive	Yield[b] (%) 2a	2aa	1a
1	$IPrAuNTf_2$ (5 mol %)	-	47	<1	7
2	$IPrAuNTf_2$ (5 mol %)	Et_3N (1 mol %)	69	<1	7
3	$IPrAuNTf_2$ (5 mol %)	Et_3N (1.5 mol %)	52	2	14
4	$IPrAuNTf_2$ (5 mol %)	Et_3N (2 mol %)	36	3	24
5	**$IPrAuNTf_2$ (6 mol %)**	**Et_3N (1 mol %)**	**88**	**<1**	**<1**
6	$Ph_3PAuNTf_2$ (6 mol %)	Et_3N (1 mol %)	70	4	<1
7[c]	CyJohnPhosAuNTf$_2$ (6 mol %)	Et_3N (1 mol %)	49	5	46
8[c]	BrettPhosAuNTf$_2$ (6 mol %)	Et_3N (1 mol %)	25	5	44
9[c,d]	(**Ar**O)$_3$PAuNTf$_2$ (6 mol %)	Et_3N (1 mol %)	12	2	75
10[e]	Au (III) (6 mol %)	Et_3N (1 mol %)	55	<1	14
11[c]	$AgNTf_2$ (10 mol %)	-	44	<5	33

[a] Reaction conditions: **1a** (0.05 mmol), $TMSN_3$ (0.1 mmol), catalyst (5-10 mol %), DCE (0.5 mL), 60 °C, in vials. [b] Measured by ^1H NMR using diethyl phthalate as the internal standard. [c] Reaction time: 24 h. [d] **Ar** = 2,4-di-*tert*–butylphenyl. [e] Dichloro(2-picolinato)gold(III).

Under the optimized reaction conditions (Table 1, entry 5), the scope of this gold-catalysed intramolecular hydroamination/ azidation reaction was then examined (Table 2). A variety of chiral homopropargyl sulfonamide substrates **1**, readily prepared by using Ellman's tertbutylsulfinimine chemistry,[7] underwent smooth tandem cyclization, leading to the corresponding 2-azide-substituted pyrrolidines **2** in mostly high yields. Besides tosyl protecting group, MBS (*p*-methoxybenzenesulfonyl) protected substrate was also suitable substrate for this reaction, delivering the expected product **2b** in 60% yield (Table 2, entry 2). In addition, other alkyl-substituted homopropargyl sulfonamides were also tolerated (Table 2, entries 3–4). Moreover, a range of aryl-substituted substrates bearing both electron-donating and electron-withdrawing groups on the phenyl ring proceeded efficiently to furnish the desired 2,5-disubstituted pyrrolidines **2e–2l** in 65-84% yields (Table 2, entries 5–12). Finally, the use of (*S*)-(+)-*tert*-butylsulfinamide-derived homopropargyl sulfonamide **1a'** also produced the desired azido-substituted pyrrolidine **2a'** with the opposite enantioselectivity (Table 2, entry 13). Of note, the enantiomeric excess (ee) was well maintained in these transformations; we determined the ee of product **2a** as a representative example (Table 2, entry 1). Significantly, high *cis* diastereoselectivity could be achieved in all cases (diastereomeric ratio (d.r.) > 10:1, determined by crude ^1H NMR spectroscopy). The molecular structure of **2j** was further confirmed by X-ray crystallography.[18]

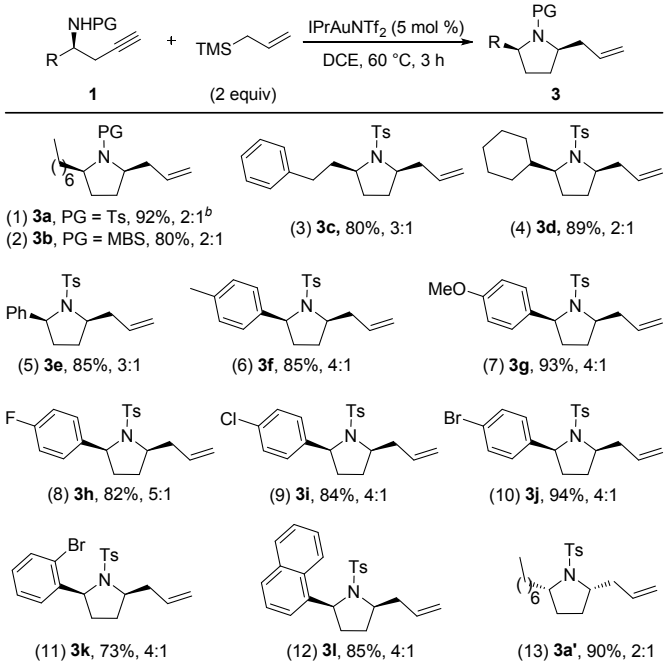
Table 2 Reaction of chiral homopropargyl sulfonamides **1** with $TMSN_3$[a]



[a] Reactions run in vials; [**1**] = 0.1 M; isolated yields are reported. [b] 99% ee, determined by HPLC on a chiral stationary phase.

Besides C-N bond formation, this gold-catalysed tandem reaction was also applicable to C-C bond formation by replacing azidosilane with allylsilane as a carbon nucleophile. As shown in Table 3, the treatment of chiral homopropargyl amides **1** with allylsilane (2 equiv) in the presence of $IPrAuNTf_2$ (5 mol %) as catalyst[17] produced the desired 2-allyl-substituted pyrrolidines **3a–3l** in 80-94% yield with up to 5:1 diastereoselectivity (Table 3, entries 1–12). It should be specially mentioned that the stereoisomers could be easily separated by column chromatography in all cases. Also, the use of (*S*)-(+)-*tert*-butylsulfinamide-derived homopropargyl sulfonamide **1a'** delivered the desired allyl-substituted pyrrolidine **3a'** in 90% yield with the opposite enantioselectivity (Table 3, entry 13). Once again, we determined the *ee* value of **3a** as a representative example (Table 3, entry 1), and found that complete chirality transfer was achieved.

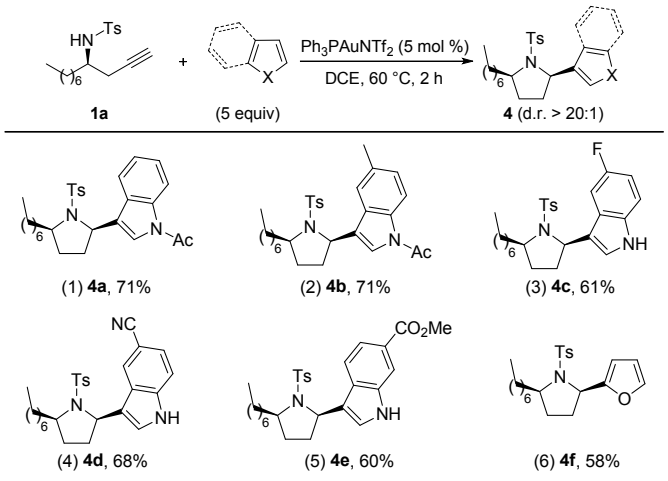
Table 3 Reaction of chiral homopropargyl sulfonamides **1** with allylsilane[a]



[a] Reactions run in vials; [**1**] = 0.1 M; isolated yields are reported. [b] 99% ee, determined by HPLC on a chiral stationary phase.

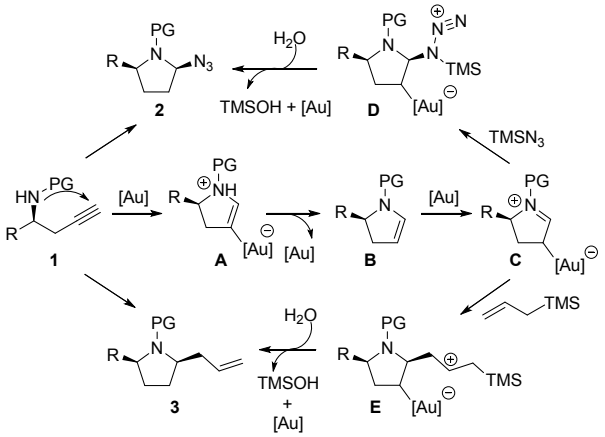
Moreover, other heterocycles were also suitable carbon nucleophiles for such a cascade cyclization, delivering the desired heterocycle-substituted pyrrolidines **4** (Table 4). The reaction of homopropargyl sulfonamide **1a** with 5 equiv of indoles in the presence of 5 mol % of $Ph_3PAuNTf_2$ instead of $IPrAuNTf_2$ as catalyst[17] afforded the corresponding 2,5- disubstituted pyrrolidines **4a**–**4e** in good yields with excellent diastereoselectivities (d.r. > 20:1). Of note, even unprotected indoles were suitable substrates for this tandem reaction when bearing electron-withdrawing groups on the indolel ring (Table 4, entries 3–5). Interestingly, this gold catalysis was also extended to the furan as a heterocycle nucleophile, and the desired 2-furan-substituted pyrrolidine **4f** was obtained in 58% yield with excellent diastereoselectivity.

Table 4 Reaction of chiral **1a** with heterocycle nucleophiles [a]



[a] Reactions run in vials; [**1a**] = 0.1 M; isolated yields are reported.

Based on our previous results[7] and experimental observations, a plausible mechanism to rationalize the formation of 2,5-disubstituted pyrrolidines **2** and **3** is proposed (Scheme 2). First, gold-catalysed intramolecular hydroamination of homopropargyl sulfonamides **1** via 5-*endo-dig* cycloisomerization generates the dihydropyrrole intermediates **B**, which are then converted into iminium intermediates **C** promoted by gold. Finally, the nucleophilic attack by the azidosilane and allylsilane to afford the desired pyrrolidines **2** and **3**, respectively. Similarly, when heterocycles serve as nucleophiles, the reaction undergoes subsequent Friedel-Crafts-type alkylation to deliver the target products **4**. Notably, the observed *cis* stereochemistry may be the result of thermodynamic control. This speculation is also supported by the fact that X-ray structure of **2j** is consistent with the *cis* product being sterically less congested than the alternative *trans* product, which is consistent with our previous results.[7]



Scheme 2 Plausible reaction mechanism.

In summary, we have developed a series of gold-catalysed intramolecular anti-Markovnikov hydroamination-initiated azidation, allylation and indolation reactions of chiral homopropargyl sulfonamides. These tandem reactions enable the rapid construction of highly functionalized pyrrolidines bearing azido, allyl and indole moiety at the 2-position. Importantly, complete chirality transfer is achieved in these cases. The use of readily available substrates, a simple procedure, and mild reaction conditions (in particular, no requirement to exclude moisture or air) render this method potentially useful in organic synthesis.[19]

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Conflicts of interest

There are no conflicts to declare.

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