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# Synthesis of Enantioenriched Pyrrolidines via Gold-Catalyzed Tandem Cycloisomerization/Hydrogenation of Chiral Homopropargyl Sulfonamides

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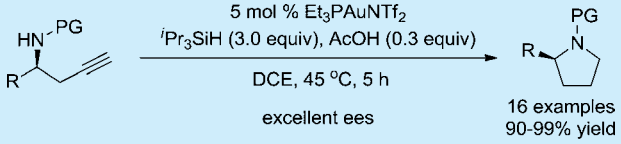
Supporting Information

**ABSTRACT:** A novel gold-catalyzed tandem cycloisomerization/hydrogenation of chiral homopropargyl sulfonamides has been developed. Various enantioenriched pyrrolidines can be obtained in excellent yields and excellent enantioselectivities by combination of chiral *tert*-butylsulfinimine chemistry with gold catalysis. Importantly, this represents the first example of a pyrrolidine synthesis from homopropargyl sulfonamide.




Chiral pyrrolidines are one of the prevalent frameworks found in numerous biologically active natural products and drugs (Figure 1)[1] and are also employed as important

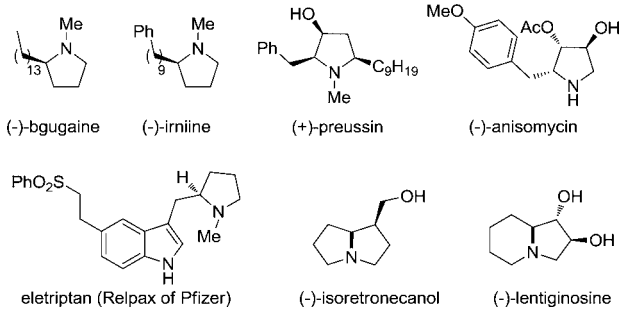
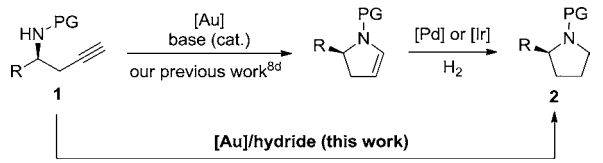



**Figure 1.** Selected examples of chiral pyrrolidines in biologically active natural products and drugs.

organocatalysts[2] and ligands[3] in organic synthesis. Although many impressive strategies have been established for the construction of the pyrrolidine motif in the past decades,[4] successful examples of enantioselective synthesis of the pyrrolidine unit remain scarce.[5] In particular, these methodologies generally suffer from drawbacks such as multistep synthesis, limited substrate scope, and inaccessible starting materials. Therefore, development of novel methods for preparation of the chiral pyrrolidine skeleton is still highly desirable, especially those with high enantioselectivity, efficiency, and flexibility.

In past decades, homogeneous gold catalysis was proven to be an extremely powerful tool for the straightforward synthesis of cyclic compounds, especially the heterocycles.[6,7] In our recent study of gold-catalyzed cycloisomerization reactions,[8] we developed a variety of gold-catalyzed cycloisomerization-initiated oxidation,[8a,b] dimerization,[8c] and halogenations,[8e] allowing the facile and efficient synthesis of various valuable heterocycles from readily available homopropargyl sulfonamides or alcohols. In addition, we also realized the direct gold-catalyzed 5-*endo*-*dig* anti-Markovnikov cycloisomerization of homopropargyl sulfonamides, leading to synthetically useful 2,3-dihydropyrroles (Scheme 1).[8d] Inspired by these results, we

**Scheme 1. Initial Design: Gold-Catalyzed Tandem Anti-Markovnikov Cycloisomerization/Hydrogenation of Chiral Homopropargyl Sulfonamides**




envisioned that by adding suitable reductants the preparation of chiral pyrrolidines **2** might be achieved through the direct gold-catalyzed tandem cycloisomerization/hydrogenation of chiral homopropargyl sulfonamides **1** (Scheme 1). Notably, pyrrolidine synthesis from 2,3-dihydropyrroles mainly relies on hydrogenation under palladium or iridium catalysis.[9] In this communication, we report herein the realization of such a gold-catalyzed tandem anti-Markovnikov cycloisomerization/hydrogenation, leading to chiral pyrrolidines in excellent yields and excellent enantioselectivities by successful combination of the chiral *tert*-butylsulfinimine chemistry[10] with gold catalysis. To the best of our knowledge, this represents the first example of a pyrrolidine synthesis from homopropargyl sulfonamide. In

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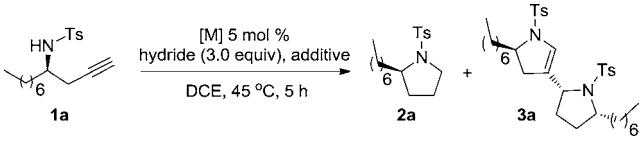
addition, the synthetic utility of this protocol was also described by the formal synthesis of natural product (−)-irniine.

At the outset, homopropargyl sulfonamide **1a** was used as the model substrate to react with various hydride sources. To our delight, it was found that the use of organosilane[11] as hydride could deliver the desired product, while other hydrides such as Hantzsch ester[12] and $NaBH_4$ failed. The treatment of substrate **1a** with 3.0 equiv of $Et_3SiH$ in the presence of 5 mol % of $Ph_3PAuNTf_2$ as gold catalyst at 45 °C in 10 h afforded the expected pyrrolidine **2a** in 50% yield, albeit together with dimer **3a** as a significant byproduct (Table 1, entry 1).[8c] We then sought

**Table 1. Optimization of Reaction Conditions**[a]



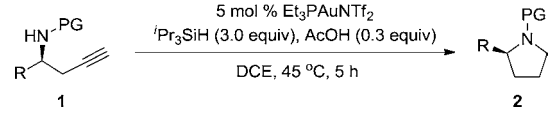

| entry | metal catalyst | hydride | additive | yield (%)[b] 2a | 3a |
|---|---|---|---|---|---|
| 1[c] | $Ph_3PAuNTf_2$ | $Et_3SiH$ | | 50 | 15 |
| 2 | $Ph_3PAuNTf_2$ | $Et_3SiH$ | AcOH (0.3) | 60 | 20 |
| 3 | $Ph_3PAuNTf_2$ | $Et_3SiH$ | AcOH (1.0) | 52 | 30 |
| 4 | $Ph_3PAuNTf_2$ | $Et_3SiH$ | TFA (0.3) | 51 | 25 |
| 5 | $Ph_3PAuNTf_2$ | $Et_3SiH$ | MsOH (0.3) | 45 | 28 |
| 6 | $Ph_3PAuNTf_2$ | $Ph_3SiH$ | AcOH (0.3) | 72 | <5 |
| 7 | $Ph_3PAuNTf_2$ | $Ph_2SiH_2$ | AcOH (0.3) | 74 | <5 |
| 8 | $Ph_3PAuNTf_2$ | $^iPr_3SiH$ | AcOH (0.3) | 89 | <1 |
| 9 | $Me_3PAuNTf_2$ | $^iPr_3SiH$ | AcOH (0.3) | 97 | <1 |
| 10 | $Et_3PAuNTf_2$ | $^iPr_3SiH$ | AcOH (0.3) | >99 | <1 |
| 11 | $XPhosAuNTf_2$ | $^iPr_3SiH$ | AcOH (0.3) | 95 | <1 |
| 12[d] | $BrettPhosAuNTf_2$ | $^iPr_3SiH$ | AcOH (0.3) | <1 | <1 |
| 13[d] | $IPrAuNTf_2$ | $^iPr_3SiH$ | AcOH (0.3) | <1 | <1 |

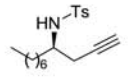
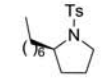
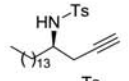
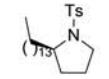
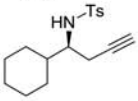
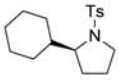
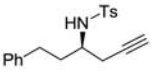
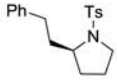
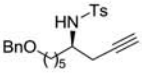
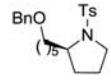
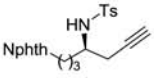
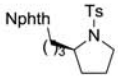
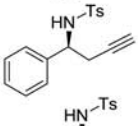
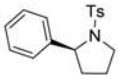
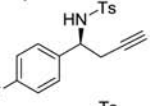
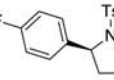
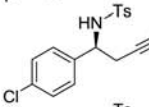
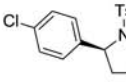
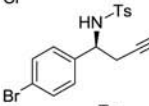
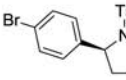
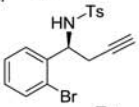
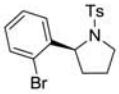
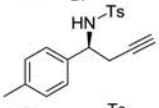
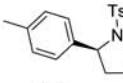
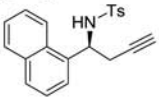
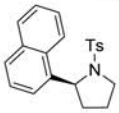
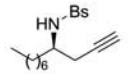
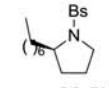
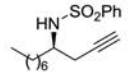
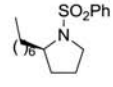
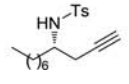
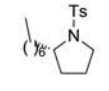
[a]Reaction conditions: [**1a**] = 0.05 M; DCE 1, 2-dichloroethane. [b]Estimated by $^1H$ NMR using diethyl phthalate as internal reference. [c]Reaction time: 10 h. [d]More than 95% of **1a** remained unreacted.

to use different equivalents and types of acids as additives (entries 2−5) and found that the reaction yield could be improved to 60% in the presence of 0.3 equiv of AcOH (entry 2). Of note, the use of acid significantly shortens the reaction time. Gratifyingly, the screening of different silanes (entries 6−8) revealed that use of triisopropylsilane completely suppressed the dimer formation, and the desired **2a** was formed in 89% yield (entry 8). Subsequently, the influence of various gold catalysts was examined (entries 9−13), and almost quantitative yield was achieved by employing $Et_3PAuNTf_2$ as gold catalyst (entry 10), while bulky gold catalysts such as $BrettPhosAuNTf_2$ and $IPrAuNTf_2$ could not catalyze this reaction (entries 12 and 13). In addition, in the absence of the gold catalyst, the desired product was not formed under the acidic reaction conditions, and $PtCl_2$ and $AgNTf_2$ also failed to catalyze such a tandem reaction.

With the optimized reaction conditions in hand, the scope of this novel gold-catalyzed cycloisomerization/hydrogenation reaction was then examined, as summarized in Table 2. All of the chiral homopropargyl sulfonamides **1**, readily prepared with excellent enantiomeric excesses by using Ellman's *tert*-butylsulfinimine chemistry, underwent smooth cycloisomerization-initiated hydrogenation, leading to the corresponding pyrrolidines **2** in excellent yields (90−99%). In particular, excellent enantioselectivities could be achieved in all cases, and

**Table 2. Reaction Scope Study**[a]




| entry | substrate | 1 | ee (%) | product | 2 | yield (%) | ee (%) |
|---|---|---|---|---|---|---|---|
| 1 |  | 1a | 99 |  | 2a | 99 | 99 |
| 2 |  | 1b | 97 |  | 2b | 95 | 98 |
| 3 |  | 1c | >99 |  | 2c | 99 | >99 |
| 4 |  | 1d | 99 |  | 2d | 97 | 99 |
| 5[b] |  | 1e | 98 |  | 2e | 97 | 97 |
| 6 |  | 1f | 97 |  | 2f | 98 | 95 |
| 7 |  | 1g | 99 |  | 2g | 99 | 99 |
| 8 |  | 1h | 98 |  | 2h | 98 | 98 |
| 9 |  | 1i | 98 |  | 2i | 98 | 98 |
| 10[c] |  | 1j | 99 |  | 2j | 98 | 99 |
| 11 |  | 1k | 97 |  | 2k | 98 | 97 |
| 12[b] |  | 1l | 99 |  | 2l | 90 | 97 |
| 13 |  | 1m | 98 |  | 2m | 99 | 97 |
| 14 |  | 1n | 99 |  | 2n | 93 | 99 |
| 15 |  | 1o | 99 |  | 2o | 97 | 99 |
| 16 |  | 1a' | 99 |  | 2a' | 98 | 99 |

[a]Reactions run in vials; [**1**] = 0.05 M; isolated yields are reported; ees are determined using HPLC on a chiral stationary phase. [b]Reaction run at 10 °C, 24 h. [c]With 5 mol % of $Me_3PAuNTf_2$, 12 h.



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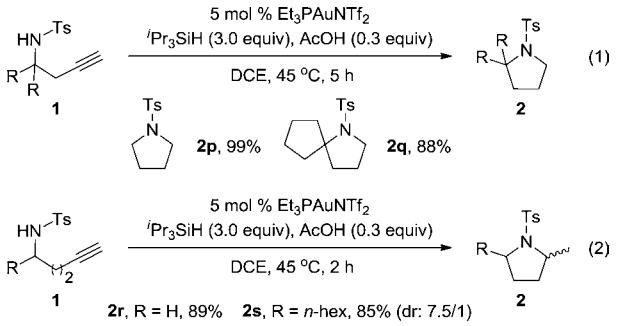
essentially no epimerization was observed, highlighting the good combination of chiral *tert*-butylsulfinimine chemistry with gold catalysis. In addition, the functional groups, such as protected hydroxy (entry 5) and *N*-phthaloyl (entry 6), were well tolerated under this cyclization reaction. Besides the tosyl group, it was found that the reaction could also proceed well for Bs (*p*-bromobenzenesulfonyl) and benzenesulfonyl-protected substrate **1n,o**, resulting in the efficient formation of the desired products **2n,o** (entries 14 and 15). Moreover, (*S*)-(+)-*tert*-butylsulfinamide-derived homopropargyl sulfonamide **1a′** also delivered the corresponding pyrrolidine **2a′** with opposite enantioselectivity (entry 16). Thus, this strategy provides a highly efficient and practical strategy for the preparation of both enantiomers of pyrrolidine derivatives just by a simple choice of the starting chiral source.

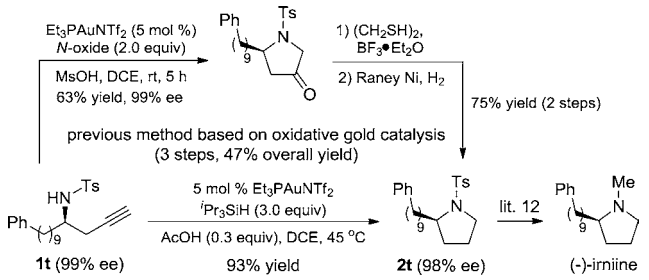
In addition, this chemistry could also be extended to the synthesis of parent pyrrolidine **2p** and spiropyrrolidine **2q** in 99 and 88% yield, respectively (eq 1). Notably, attempts to extend




the reaction to 4-pentyn-1-amides only resulted in the formation of 2-methyl pyrrolidines **2r,s** in excellent yields presumably via gold-catalyzed 5-*exo*-*dig* Markovnikov cycloisomerization/hydrogenation (eq 2).

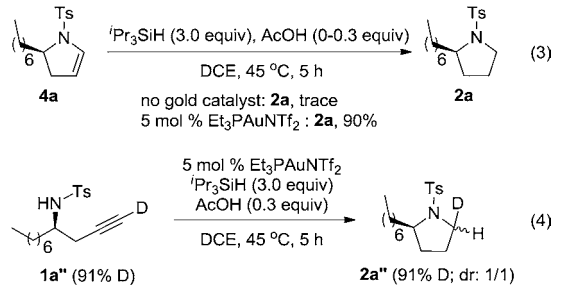
The utility of this methodology was further demonstrated in the formal enantioselective synthesis of (−)-irniine (Scheme 2).[13] Starting from chiral homopropargyl sulfonamide **1t**, the

**Scheme 2. Formal Enantioselective Synthesis of (−)-Irniine**




tandem sequence mentioned above furnished the desired pyrrolidine **2t** in one step in 93% yield, which could be transformed into the natural product (−)-irniine.[14] It is worth mentioning that starting from the same substrate **1t**, the synthesis of **2t** demands three steps with low efficiency (47% overall yield) according to our previously reported method based on oxidative gold catalysis.[14]

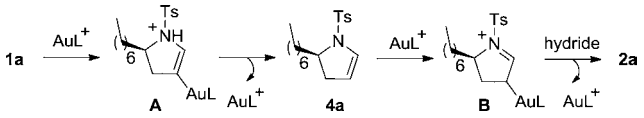
To explore the reaction mechanism, several control experiments were conducted. As shown in eq 3, the treatment of 2,3-dihydropyrrole **4a**[8d] with $^{i}Pr_3SiH$ could deliver the desired pyrrolidine **2a** in 90% yield only in the presence of gold catalyst. In addition, a deuterium labeling study revealed that almost no




deuterium loss was observed when deuterium-labeled **1a** (91% D) was treated under the optimal conditions (eq 4). These results indicate the reaction is presumably initiated by a gold-catalyzed 5-*endo*-*dig* cycloisomerization but does not go through the gold vinylidene intermediate pathway.

On the basis of these experimental observations, a plausible mechanism to rationalize the formation of **2a** is proposed (Scheme 3). The reaction may initially involve a gold-catalyzed

**Scheme 3. Plausible Reaction Mechanism**




direct 5-*endo*-*dig* cycloisomerization, followed by the in situ generation of intermediate **4a**, which is quickly converted into iminium intermediate **B** catalyzed by gold and acid. In other words, gold serves dual functions in this tandem reaction. Finally, the iminium species undergoes facile reduction by hydride to afford the target product **2a**.

In summary, we have developed a practical and general method for the enantioselective synthesis of various pyrrolidines through gold-catalyzed tandem anti-Markovnikov cycloisomerization/hydrogenation of chiral homopropargyl sulfonamides, which represents the first example of a pyrrolidine synthesis from homopropargyl sulfonamide. Moreover, this chemistry combines the homogeneous gold catalysis well with the organosilane reduction, which has been rarely reported.[15] Importantly, gold serves dual catalytic roles in such a tandem sequence. In addition, its synthetic application has also been demonstrated by a formal synthesis of (−)-irniine in a highly efficient and concise manner.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02736.

Experimental procedures and spectral data for all new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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