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# Gold-Catalyzed 1,2-Migration of Silicon, Tin, and Germanium en Route to C-2 Substituted Fused Pyrrole-Containing Heterocycles

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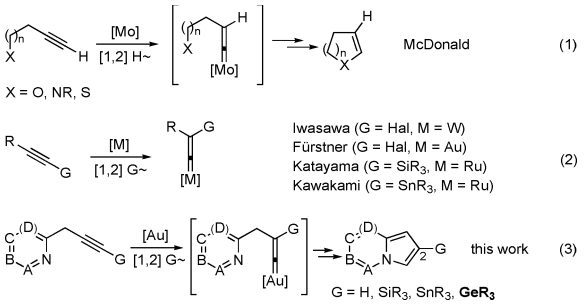
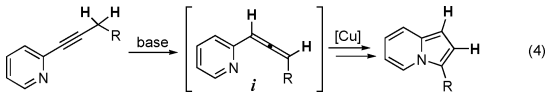
Alkyne−vinylidene isomerization is a mechanistically interesting[1] and synthetically useful transformation.[2] For example, McDonald used this transformation as the key step in efficient synthesis of heterocycles (eq 1).[3] It has also been shown that various groups (G) can undergo 1,2-migration upon alkyne−vinylidene isomerization, as demonstrated by Iwasawa (G = Hal, M = W),[4] Fürstner (G = Hal, M = Au),[5] Katayama (G = $SiR_3$, M = Ru),[6] and Kawakami (G = $SnR_3$, M = Ru)[7] (eq 2). However, to the best of our knowledge, no examples of synthesis of heterocycles with 1,2-migration of groups other than H have ever been reported. Thus, we reasoned that development of alternative routes toward heterocycles, which proceed with 1,2-group migration, would be desirable, as they would allow for the synthesis of densely substituted molecules. Herein, we wish to report a new Au-catalyzed cascade cycloisomerization of propargylic derivatives of N-containing heterocycles into fused pyrrole-containing heterocycles. The cascade transformation involves 1,2-migration of silyl-, stannyl-, and even the *previously unknown migration of a germyl group* and allows for efficient synthesis of various fused pyrroloheterocycles functionalized at position C-2 (eq 3).

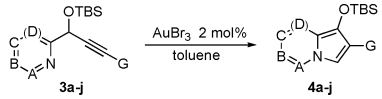


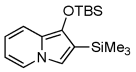
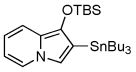
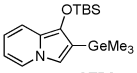
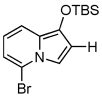
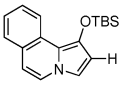
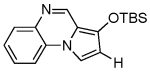
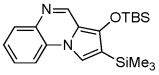
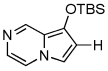
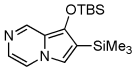
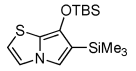

We have recently reported the cycloisomerization of alkynylpyridines into indolizines (eq 4).[8] The reaction proceeds via a base-assisted propargyl−allenyl isomerization to intermediate ***i***, followed by its cyclization into the indolizine core. This transformation presumes two formal hydrogen migrations, and thus is limited to the preparation of C-1,2 unsubstituted indolizines.



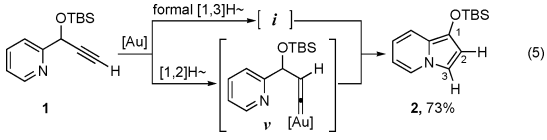

Naturally, as we were interested in developing approaches toward C-1 substituted heterocycles, we turned our attention to the cycloisomerization of easily available[9] nonconjugated propargylpyridine **1** (eq 5). After catalyst optimization,[10] it was found that **1**, in the presence of Au(I) or Au(III) salts,[11] undergoes smooth cycloisomerization into C-1 substituted indolizine **2**. It is reasonable to propose that this transformation operates through allenyl intermediate ***i*** (e.g., via another mode of the propargyl−allenyl cycloisomerization depicted in eq 4). Alternatively, this reaction may proceed via isomerization of terminal alkyne **1** into gold−vinylidene intermediate ***v***, which subsequently cycloisomerizes into the heteroaromatic structure **2** (eq 5).

***Table 1.*** Synthesis of Fused Pyrrole-Containing Heterocycles




| # | G | T (°C) | Time, h | Product | | Yield, %[a] |
|---|---|---|---|---|---|---|
| 1 | $SiMe_3$ | 50 | 1.5 |  | **4a** | 63[b] |
| 2 | $SnBu_3$ | 50 | 0.5 |  | **4b** | 64[d] |
| 3 | $GeMe_3$ | 25 | 0.5 |  | **4c** | 92[b] |
| 4 | H | 50 | 1.5 |  | **4d** | 62 |
| 5 | H | 25 | 0.5 |  | **4e** | 81 |
| 6 | H | 50 | 2.0 |  | **4f** | 94 |
| 7 | $SiMe_3$ | 50 | 4.0 |  | **4g** | 78 |
| 8 | H | 60 | 4.5 |  | **4h** | 72 |
| 9 | $SiMe_3$ | 25 | 0.5 |  | **4i** | 87[e] |
| 10 | $SiMe_3$ | 50 | 3.5 |  | **4j** | 56 |

[a] Isolated yield; reactions performed in 0.5 mmol scale. [b] Yield over 2 steps. [c] Reaction was performed in 5.0 mmol scale in the presence of AuCl catalyst (0.5 mol %). [d] NMR yield. [e] AuCl was used as a catalyst.

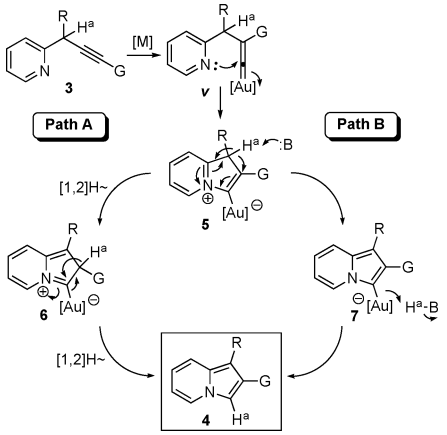



To clarify whether this reaction proceeds via an allenyl (***i***) or vinylidene (***v***) intermediate, we examined cycloisomerization of TMS-substituted propargylpyridine **3a** in the presence of Au-catalyst. It was hypothesized that a prototropic isomerization (via intermediate ***i)***[12] would lead to indolizine with the silyl group



10.1021/ja063278l CCC: $33.50 

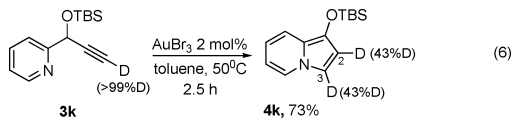
***Scheme 1.*** Proposed Mechanism for Cascade Cycloisomerization




attached to the C-3 position, whereas the silyl group would be at C-2 if alkyne−vinylidene isomerization operates (via intermediate ***v***). To our great delight, it was found that **3a**, in the presence of $AuBr_3$ (2.0 mol %) in toluene at 50 °C, underwent smooth cycloisomerization to afford indolizine **4a** with TMS group migration to the C-2 position, as the sole regioisomer in 63% yield (Table 1, entry 1). It deserves mentioning that in indolizines, the C-2 site is an unfunctionalizable position, and its substituent has to be introduced prior to cyclization.[13]

Motivated by the importance of differently substituted fused pyrroloheterocycles,[14] and encouraged by the successful cycloisomerization of TMS-containing substrate **3a**, we examined various propargyl heterocycles in this transformation (Table 1). Gratifyingly, the stannyl group, known to undergo migration upon alkyne−vinylidene isomerization[7] (entry 2), underwent smooth migration to give 2-stannyl indolizine **4b** in good yield. Remarkably, we also found that unprecedented 1,2-germyl migration can also occur to produce 2-germylindolizine **4c** in excellent yield (entry 3). Notably, this cycloisomerization appeared to be general with regard to the heterocyclic core. Other heterocyclic systems, such as isoquinoline (entry 5), quinoxaline (entries 6 and 7), pyrazine (entries 8 and 9), and thiazole (entry 10), reacted smoothly, producing fused pyrroloheterocycles in good to excellent yields.

We propose the following mechanistic rationale for this novel transformation. First, isomerization of alkyne **3** results in the formation of vinylidene ***v***[15] (Scheme 1), followed by nucleophilic attack of the nitrogen lone pair at the vinylidene carbon, resulting in formation of zwitterion **5**. The latter can either undergo a series of 1,2-hydride shifts (path A), or a deprotonation−protonation sequence (path B) to furnish **4**.[16] To verify which mechanism operates, we performed a deuterium-labeling experiment utilizing isotopically homogeneous propargyl pyridine **3k**. It was found that under standard cycloisomerization conditions, the reaction produced indolizine **4k** with equal distribution of deuterium between positions C-2 and C-3,[17] thus strongly supporting path A.[18]




In summary, we have developed a new mild cascade cycloisomerization of propargyl N-containing heterocycles into various types of N-fused pyrroloheterocycles in the presence of gold catalyst. The reaction proceeds via alkyne−vinylidene isomerization with concomitant 1,2-migration of H, silyl-, and stannyl groups, as well as previously unknown 1,2-migration of a germyl group, giving easy access to a variety of C-2 functionalized heterocycles.

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**Supporting Information Available:** Preparative procedures, analytical and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) See, for example (a) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648. (b) McDonald, F. E.; Burova, S. A.; Huffman, L. G. *Synthesis* **2000**, 970.
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(9) See Supporting Information for details.
(10) Employment of Cu(I) salts led to trace amount of products, whereas various Ag, Pt, and Pd sources tested did not catalyzed this reaction at all.[9]
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(12) For Au-catalyzed propargyl−allenyl prototropic isomerization, see ref 11c.
(13) For review, see for example Behnisch, R.; Behnisch, P.; Eggenweiler, M.; Wallenhorst, T. *Indolizine;* In Houben-Weyl E6a/2a; Thieme: New York, 1994; p 323.
(14) For pharmacologically important indolizines, see, for example (a) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636. (b) Schoeffter, P.; Hoyer, D. Naunyn-Schmiedeberg's *Arch. Pharmacol.* **1989**, *339*, 675. (c) Gundersen L.-L.; Malterudb K. E.; Negussiea A. H.; Risea F.; Teklua S.; Østby O. B. *Bioorg. Med. Chem.* **2003**, *11*, 5409.
(15) Au(I) is most likely the active catalyst. In the case of employment of $AuBr_3$ as a precatalyst, the latter can be reduced to Au(I) species via various redox processes. See ref 11b for discussion.
(16) A referee pointed out possible Au-catalyzed C-3 → C-2 TMS group migration after cyclization, and brought to our attention a reference on Au-catalyzed migration of alkyl group in indole series: Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem.* **2005**, *70*, 2265. However, a test experiment with pyrroloquinoxaline **8**, C-3 TMS analogue of **4g**, ruled out this possibility.[9]
(17) Control experiment indicated no deuterium scrambling between **4h** and $D_2O$ occurred under the same reaction conditions.[9] For deuterium scrambling in N-unsubstituted pyrrole ring in the presence of Au(I) complexes, see ref 11h.
(18) Equal distribution of deuterium between positions C-2 and C-3 is possible via path A if there is no H/D kinetic isotope effect (transformation **6** to **4**). Obviously, path B cannot explain the observed scrambling of deuterium at C-2.

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