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Gold(I)/Copper(II)-Cocatalyzed Tandem Cyclization/Semipinacol Reaction: Construction of
6-Aza/Oxa-Spiro[4.5]decane Skeletons and Formal Synthesis of (±)-Halichlorine
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Construction of Aza/Oxa-Spirocyclic Skeletons. Formal Synthesis of (±)-Halichlorine

Significance: Aza/Oxa-spirocyclic skeletons are key structural motifs found in a number of bioactive natural products (see Reviews 1 and 2 below). Reported is a Au(I)/Cu(II)-cocatalyzed sequential intramolecular cyclization–semipinacol rearrangement for the construction of 6-aza/oxa-spiro[4.5]-decane skeletons from functionalized ynones. Mono- and disubstitution at the C-4 or C-5 positions is tolerated. The reaction proceeds with excellent diastereoselectivity to give the corresponding products as single diastereomers. However, the ynone starting materials are not readily available, and their syntheses require multiple (five to seven) steps. The utility of this methodology was demonstrated in the formal synthesis of (±)-halichlorine from aza-spirocyclic **1**.

Comment: Numerous strategies have been developed for the construction of aza/oxa-spirocyclic skeletons (see Reviews 3 and 4 below). Most of these approaches are based on a stepwise construction of the quaternary carbon center followed by formation of the hetero- or carbocycle. The present methodology allows one-pot syntheses of various aza/oxa-spirocycles from functionalized ynones. Mechanistic studies indicate that the reaction proceeds through an initial Au(I)-catalyzed 6-endo-dig cyclization to generate intermediate **A**, which subsequently undergoes a Cu(II)-catalyzed semipinacol rearrangement to afford the spirocyclic product.

Reviews: D. L. J. Clive, M. Yu, J. Wang, V. S. C. Yeh, S. Kang *Chem. Rev.* **2005**, 105, 4483–4514; S. M. Weinreb, M. F. Semmelhack *Acc. Chem. Res.* **1975**, 8, 158–164; S. A. A. El Bialy, H. Braun, L. F. Tietze *Synthesis* **2004**, 2249–2262; G. Dake *Tetrahedron* **2006**, 62, 3467–3492.

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