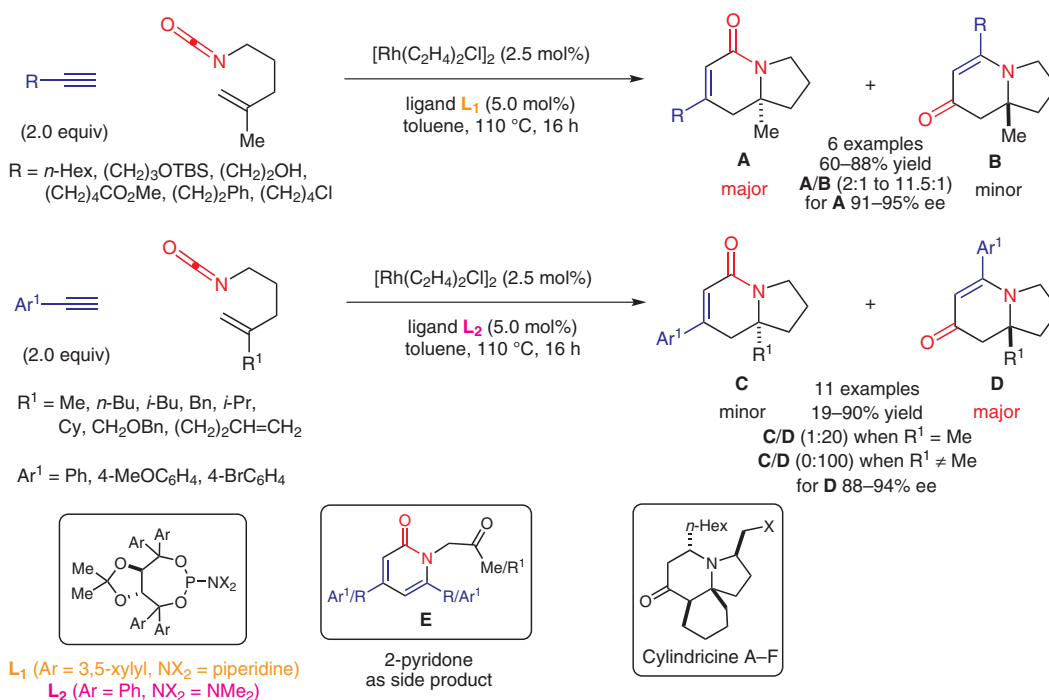


Rhodium-Catalyzed Enantioselective Cycloaddition Route to Indolizidines



Significance: Described herein is a synthesis of indolizidines by an asymmetric Rh(I)-catalyzed [2+2+2] cycloaddition of 1,1-disubstituted alkenyl isocyanates to terminal alkynes. The reaction proceeds in moderate to high yields with a high level of enantio- and regioselectivity in the presence of the phosphoramidite ligands. Aliphatic alkynes gave lactams **A** as major products whereas vinylogous amides **B** predominated with aryl alkynes. The formation of 2-pyridones **E** as the major byproduct was suppressed under high dilution reaction conditions (typically 0.04 M). The isolated yields were low with sterically demanding substituents (e.g., R^1 = *i*-Pr, Cy) and in such reactions an increase in the 2-pyridone byproduct was observed, presumably due to a slow rate of coordination–insertion of the alkene with Rh.

Comment: The indolizidine and quinolizidine framework are present in many biologically important natural products (J. R. Lindell *Nat. Prod. Rep.* **2002**, 773; J. P. Michael *Nat. Prod. Rep.* **2007**, 191), for example, marine alkaloids cylindricine A–F (see review below). This present work constitutes an extension of the methodology previously applied by the Rovis group in the synthesis of the natural product (+)-lasubine II demonstrating the use of this methodology (*J. Am. Chem. Soc.* **2006**, *128*, 12370). The scope of the reaction was reasonably well established.

Review: S. M. Weinreb *Chem. Rev.* **2006**, *106*, 2531-2549.