Gold-Catalyzed Hydroamination of Methylene Cyclopropanes in Enantioselective Drug Synthesis

Zhen, Christopher

Enantioselective drug synthesis is a critical research problem as evidenced by the billions of funding the field gets. In this research, a novel method of enantioselectively synthesizing drugs was developed based on research by Yamaguchi et al which showed that a cyclopropane derivative of a drug can effectively lock the conformation of a drug and limit it to a single enantiomer.1 This research focuses on a reaction using a novel gold-based catalyst MeCnAuP(Cy2-o-biphenyl)SbF6 to add functional groups to 1-phenyl-methylenecyclopropane. One product of the reaction added the nucleophile (1-methyl-2-imidazolidinone) across the methylene, keeping the cyclopropane ring intact. This product was both unexpected, as previous literature had all documented the opening of the ring, and desired as the intact ring allows for a simple reaction to create cyclopropane derivatives. Even more promising, after decreasing the reaction temperature from 100°C to 60°C, the reaction was biased in a 1.5:1 ratio towards the desired product (57% yield). Overall, data show that this technique is effective in adding amines to cyclopropane rings in moderate yields and future research can focus on adding different functional groups and increasing yields. This would allow researchers to make conformationally restricted cyclopropane derivatives and consequently more effective, enantioselective drugs [1] Yamaguchi, K., Kazuta, Y., Hirano, K., Yamada, S., Matsuda, A., & Shuto, S. (2008). Synthesis of 1-arylpiperazyl-2-phenylcyclopropanes designed as antidopaminergic agents: cyclopropane-based conformationally restricted analogs of haloperidol. Bioorganic & medicinal chemistry, 16(19), 8875–81. doi:10.1016/j.bmc.2008.08.061

Awards Won: