# Synthesis of Spiro Ethers by Double $S_N2$ Reaction of α-Chloroketones

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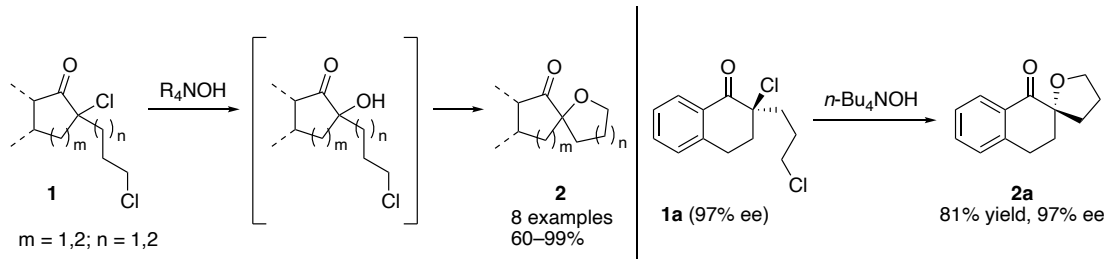
Spirocycles are important scaffolds in drug discovery, mainly due to their conformational rigidity and unique three-dimensional structures.[1] Indeed the spiro ether core which is found in a wide range of biologically actives molecules is an attractive subclass of spirocycles with a diverse array of medicinal applications.

We recently reported that decarboxylative chlorination of β-keto acids afforded α-chloroketones with high enantioselectivity in presence of chiral primary amine catalyst.[2] We also found that subsequent $S_N2$ reaction of the resulting α-chloroketones with quaternary ammonium hydroxide yielded tertiary α-hydroxyketones without loss of enantiopurity.[3] Based on our previous results, we envisaged that intramolecular $S_N2$ reaction of α-hydroxyketones would afford spiro ethers when a suitable leaving group is introduced at the terminal of side chain in the substrate.

Firstly, we prepared racemic α-chloroketones **1** with a chlorine atom at the terminal of side chain. Then, α-chloroketones **1** was treated with quaternary ammonium hydroxide to give the desired spiro ethers in up to 99% yield. The reaction is considered to proceed by intermolecular $S_N2$ reaction to yield α-hydroxyketones and subsequent intramolecular $S_N2$ reaction. The method provides various spiro ethers with 5/5-, 5/6-, 6/5, and 6/6-spiro ring systems. Next, we prepared an enantiomerically enriched α-chloroketone **1a** by decarboxylative chlorination of corresponding β-keto acid with 97% ee.[2] Treatment of **1a** with quaternary ammonium hydroxide successfully yielded the corresponding spiro ether **2a** without loss of enantiopurity.

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