Stereoselective synthesis of sterically hindered 17α-methyl steroid derivatives from malononitriles via oxidative functionalization under O_2

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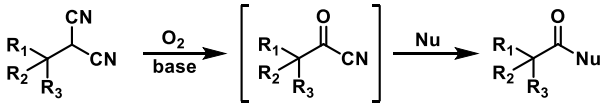
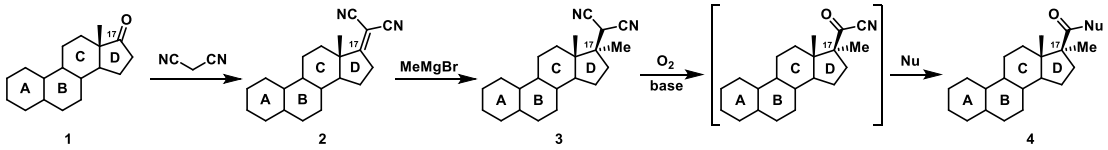
Synthesis of steroid derivatives with methoxycarbonyl and methyl groups at C17 is difficult because of the steric hindrance of the two contiguous quaternary chiral centers.[1] On the other hand, we previously reported that malononitrile derivatives react with molecular oxygen and nucleophile to afford the carbonyl compounds (Scheme 1).[2] Herein, a new, convenient stereoselective synthesis of sterically hindered 17α-methyl steroid derivatives was realized via our previously developed oxidative functionalization.

The substrates were prepared from 17-keto steroids **1** by Knoevenagel condensation with malononitrile (Scheme 2). The Knoevenagel products **2** then underwent a stereoselective 1,4-addition with methyl Grignard reagent to obtain 17α-methyl steroid derivatives **3**. A subsequent oxidative functionalization with various nucleophiles and a base under the atmosphere of oxygen gave the corresponding steroid derivatives **4** in a high yield. Sterically hindered ester, ketone, amide and thioester could be synthesized efficiently with high diastereoselectivity.

Scheme 1:



Scheme 2:



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