Chiral Phosphoric Acid Catalyzed Enantioselective Addition of Thiols to *in Situ* Generated Ketimines: Synthesis of *N,S*-Ketals

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Abstract:

N,S-acetals are important structural motifs found in many drugs and natural product molecules.[1] *N,S*-Acetals have been investigated as cell growth inhibitors (**1**), sedatives (**2**), antibacterials (**3**), and HIV inhibitors (**4**). The isoindolinone molecule (**4**) having *N,S*-kcetal motif, a known HIV-1 reverse transcriptase inhibitor[5] is of particular importance (Figure 1).[2] The main catalytic synthetic method used for accessing chiral *N,S*-acetals involves, 1,2-addition of thiols to imines, *α*-sulfenylation and *α*-amination of substituted rhodanines.[3]

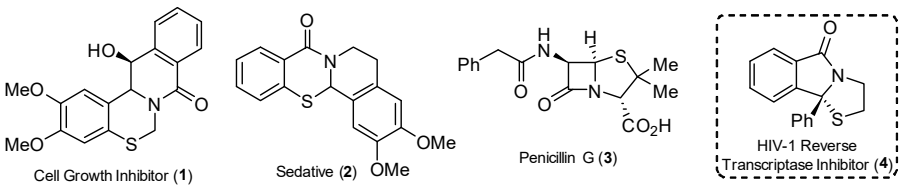
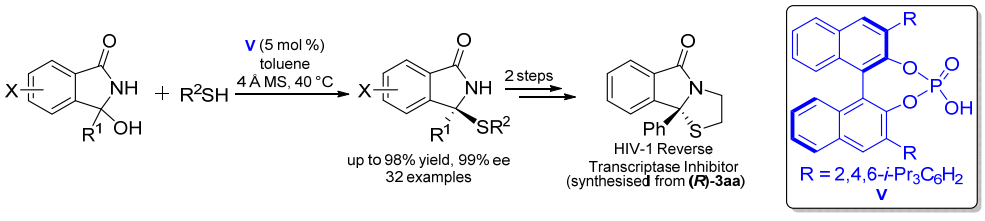


Figure 1: Examples of useful *N,S*-acetals and *N,S*-ketals

Toward this, we have developed the chiral Brønsted acid catalyzed enantioselective 1,2-addition of thiols to *in situ* generated ketimines, derived from 3-hydroxyisoindolinones.[3] The protocol provides a variety of isoindolinone-derived *N,S*-ketals in up to 98% yield and up to 99% enantioselectivity. The products have been converted to a known non-nucleoside HIV-1 reverse transcriptase inhibitor and a 1,3-thiazine derivative (Scheme 1).



Scheme 1: Brønsted acid catalyzed enantioselective synthesis of isoindolinone-derived *N,S*-ketals

References and Notes:

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