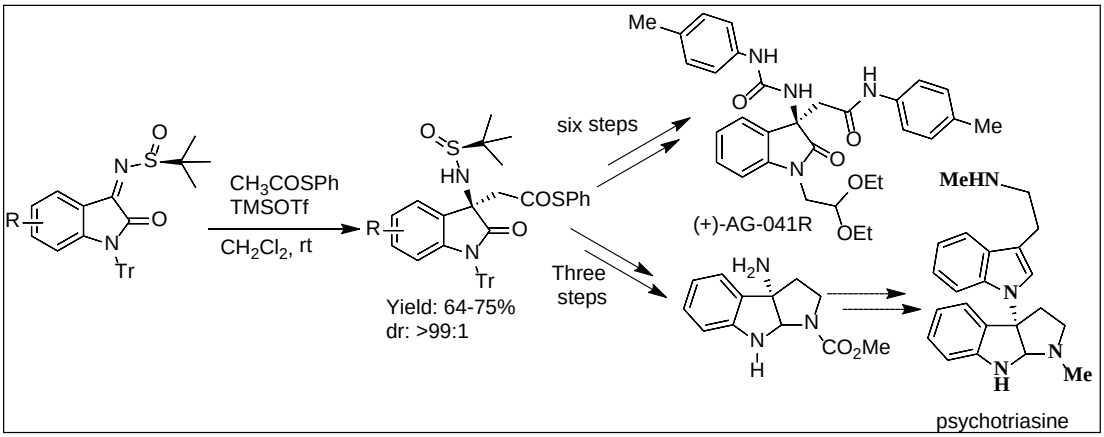
Studies towards Asymmetric Synthesis of Bioactive Oxindole Compounds: Synthesis of (+) AG-041R, (-) Psychotriasine, ABC ring of Cyanogramide and Pyrrolindonyl Spiroxindole

The 3-3′ oxindole framework is considered as a privileged heterocyclic motif, as it is present in many bioactive natural products and in a series of pharmaceutically active compounds. The significant bioactivities and versatility of these compounds propelled us to develop newer methodologies for the asymmetric synthesis of 3,3′-disubstituted oxindoles and their application synthesis imporrtant natural products and drug leads.

3-Subtituted-3-amino-2-oxindoles such as indole based $\beta^{3,3}$-amino acid derivatives are privileged structural motifs that are found in numerous pharmaceuticals and can also serves as important precursors in synthesis of pyrroloindoline alkaloids. A highly efficient TMSOTf-mediated asymmetric Mukiayama-acetate-Mannich reaction of isatin derived chiral *N-tert*-butanesulfinyl ketimines and *S*-phenyl thioacetate was developed to afford the direct synthesis of indole-based $\beta^{3,3}$-amino acid thioester with excellent selectivity (dr >99:1). Synthesis of (+)-AG-041R, formal synthesis of (-) psychotriasine and reagent-free peptide coupling have been accomplished utilizing the developed method.

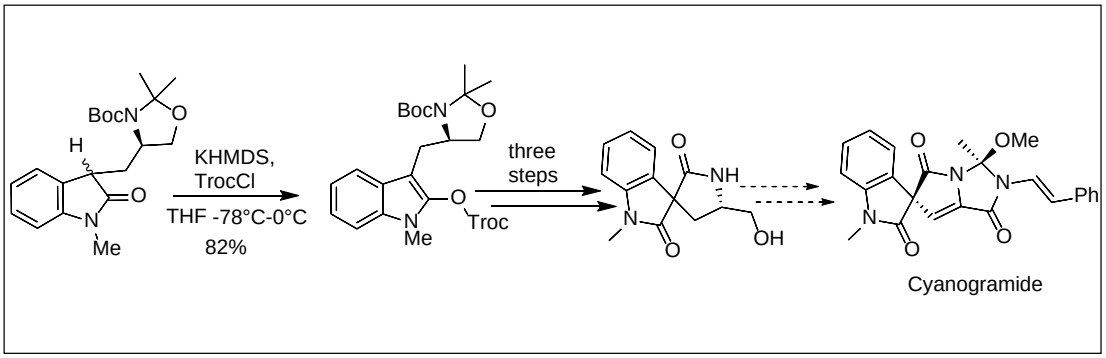
Scheme 1 Mukiayama Mannich reaction chiral isatin derived ketimines.



Recently an unprecedented pyrrolidonyl spiroxindole alkaloid, cyanogramide was isolated having a 3,3′-oxindole skeleton. It exhibits reversal effect towards P-gp-mediated multidrug resistance and shows a significant cytotoxic effect. The remarkable bioactivity and interesting structure of cyanogramide allured us to attempt its total synthesis and to synthesize pyrrolidonyl spiroxindole compounds for their bioactivity study.

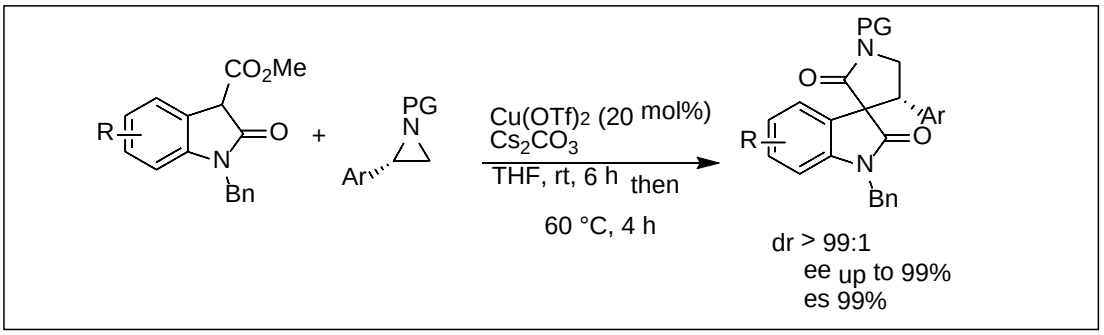
After overcoming various initial failures, we are able to synthesize dihydro ABC ring of cyanogramide utilizing a carboxyl migration reaction followed by spiro lactamization. The synthesized pyrrolidonyl spiroxindole is an advanced key intermediate in the synthesis towards cyanogramide.

Scheme 2 Synthesis of dihydro ABC ring of cyanogramide.



The pyrrolidonyl spiroxindole is an unique skeleton present in cyanogramide and few bioactive compounds. Synthesis and the biology of pyrrolidonyl spirooxindoles are sparely explored. We have developed a highly efficient one-pot protocol for the asymmetric synthesis of pyrrolidonyl spiroxindoles with excellent selectivity (dr: >99:1 and ee upto 99%) via domino aziridine opening and lactamization reaction of oxindole ester with chiral aziridine.

Scheme 3 Domino aziridine opening and spirolactamization reaction.



With the developed domino reaction, we have synthesized a small library (twenty-two) of pyrrolidonyl spiroxindoles and tested for anti-inflammatory and anticancer activity. Among these, one compound showed promising anticancer activity.(**IC_{50} of 10 μM**).

Keywords: *3-3′ oxindole, asymmetric Mukiayama-acetate-Mannich reaction, (+)-AG-041R, (-) psychotriasine, reagent-free peptide coupling, pyrrolidonyl spiroxindole, alkaloid, cyanogramide, aziridine opening,*