Enantioselective Iodocycloetherification by Lewis Base/Chiral Brønsted Acid Cooperative Catalysis

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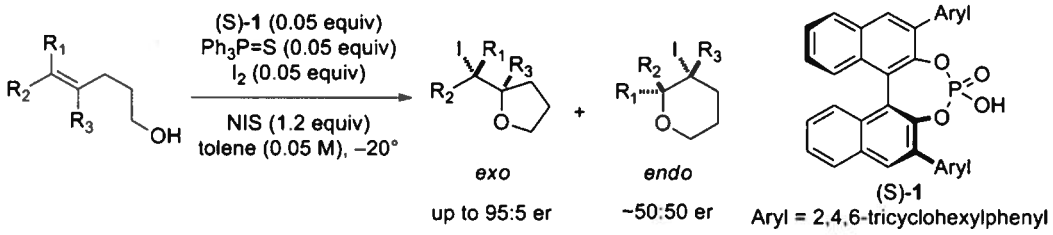
Cooperative Lewis base/chiral Brønsted acid catalysis is employed to promote the formation of iodiranium ions and the enantioselective trapping of these intermediates with pendant alcohols. *N*-iodosuccinimide (NIS) was found to be critical to the enantioselectivity as the stoichiometric iodine source. The use of catalytic amounts of BINOL-derived phosphoric acid **1** with $Ph_3P{=}S$ affords greater reactivity and selectivity than with **1** alone. The presence of catalytic iodine also increases reactivity without detriment to the enantio- or *exo:endo* selectivity.

Aryl and aliphatic 5-substituted *Z*-alk-4-enols and aliphatic *E*-alk-4-enols cyclize with high *exo* selectivity. The cyclization of 5-aryl substituted *E*-pentenols results in a mixture of exo and endo cyclization products. Tetrahydrofurans produced via this protocol are enantioenriched while the tetrahydropyrans generated are nearly racemic.



Improving the Process Route and Metabolic Stability of the Anticancer Compound PAC-1

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PAC-1 is an *ortho*-hydroxy-*N*-acylhydrazone that induces apoptosis in cancer cells by chelation of antiapoptotic zinc. Preliminary results indicate the potential for anticancer efficacy with **PAC-1**, and this potential is currently being investigated in various mouse, rat, and dog models of cancer. In order to facilitate these efforts, an improved process route towards **PAC-1** has been developed, which allows for the synthesis of 140-gram batches of compound in a relatively short time period of 1-2 weeks. A second goal of the project is the development of **PAC-1** analogues with enhanced metabolic stability. In order to achieve this goal, a combinatorial library of 45 **PAC-1** analogues has been synthesized, with substitutions designed to resist metabolic transformations. The new analogues have been evaluated in cell culture and liver microsomes. In general, the novel derivatives retain anticancer activity, and each modification was successful in blocking the undesired metabolic transformation.