Carbon-Carbon Bond Forming Reactions in Heterocycle Synthesis, Elaboration, and Biomedical Applications

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In this seminar the application of tert-butanesulfinamide chemistry and C-H bond functionalization to the synthesis and elaboration of heterocycles will be presented.

**tert-Butanesulfinamide Chemistry**

tert-Butanesulfinamide (1) methodology developed in my labs is now extensively used by pharma for the preparation of amine-containing compounds as evidenced by the more than 320 patents that have been filed where the reagent has been used in the discovery or large scale production of drug candidates. The application of tert-butanesulfinamide methodology to the first asymmetric total synthesis of tubulysin D will be described. Tubulysin D is an exceptionally potent cell growth inhibitor that acts by inhibiting tubulin polymerization, thus inducing apoptosis with activity exceeding that of the anti-cancer drugs vinblastine, paclitaxel, and the epothilones. Polymer conjugates of simplified analogues of tubulysin D that show efficacy in the treatment of cancer in animal models will also be described.

**C-H Bond Functionalization**

C-H bond functionalization provides many opportunities for the rapid assembly of complex architectures from simple precursors. An array of transformations have been developed based upon the directed alkylation or alkenylation of aromatic or α,β-unsaturated imines via C-H bond activation, including catalytic enantioselective transformations and cascade reactions. An overview of this chemistry will include efficient asymmetric syntheses of complex heterocyclic natural products by imine-directed intramolecular alkylation.

The direct alkylation and arylation of nitrogen heterocycles, which proceeds through a novel substrate-derived metal-bound N-heterocyclic carbene (NHC) intermediate, will also be presented. Discussion of this new type of C-H bond functionalization will include the design of a class of air stable bidentate phosphine-olefin ligands for the extremely functional group tolerant direct arylation of nitrogen heterocycles and also the first examples of catalytic enantioselective intramolecular heterocycle alkylation.

References
