Development of $Hg(OTf)_2$-Catalyzed Reaction and Development of a Potent Immunostimulating Compound Vizantine

Mugio Nishizawa
(Faculty of Pharmaceutical Sciences, Tokushima Bunri University)

We have introduced $Hg(OTf)_2$ as a new catalyst for organic synthesis based on its very high activity. In particular, the high affinity for the alkynyl moiety led us to develop a variety of reactions initiated from alkynes. Hydration, C-C bond forming cyclization, and heterocycle syntheses have been achieved with very high catalytic efficiency under mild conditions. The first mercuric salt-catalyzed olefin cyclization, including aryl allyl alcohol cyclization and nitrogen allyl alcohol cyclization, has also developed by the introduction of the allylic hydroxyl group as the protonation site. Because the allyl alcohol cyclization generates a new chiral center, catalytic asymmetric cyclization was also examined. Asymmetric induction was achieved with up to 97% ee. Furthermore, on the basis of our finding that a single OTf group on Hg is sufficient for the catalytic cycle, the first solid-supported mercuric salt, silaphenylmercuric triflate, was also developed and found to act as a powerful catalyst for most $Hg(OTf)_2$-catalyzed reactions.

Trehalose-6, 6'-dimycolate (TDM), previously known as cord factor, is a glycolipid distributed in the cell wall of *Mycobacterium tuberculosis* that displays anti-tumor activity on account of its immunoadjuvant profile. Unfortunately, the significant toxicity of TDM prevents the therapeutic application of this compound. We have carried out synthetic studies to develop analogues of TDM with reduced toxicity and greater biological activity over the parent compound. By achieving the synthesis of related trehalose diester, trehalose-6, 6'-dicorynomycolate (TDCM), the stereochemistry of natural TDCM was elucidated. Through the synthesis of more than 100 TDCM analogues, we have reached a simple TDCM derivative that induces a release of cytokines such as MIP-2, IL-17, and IFN-γ more potently than TDCM without release of TNF-α. This compound activates phagocytosis and superoxide production in macrophages. Moreover, the analogue is drastically less toxic and dose not induce a cytokine storm. The new immunostimulating compound was named vizantine. *In vivo* studies have shown vizantine to display remarkable anti-metastasis activity using breast cancer FM3A cells and anti-infectious disease activity against *Clostridium perfringens* and *Pseudomonas aeruginosa*. Vizantine, therefore, is a novel drug candidate with potent immunostimulating activity that shows potential for the treatment of cancer and infectious diseases.