26G-ISMS14 **Development of an Oxidative Mizoroki-Heck Reaction for Late-stage C-H Functionalization of Complex Molecules and Application to Pharmaceutical Studies**

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Duloxetine, a serotonin and noradrenaline reuptake inhibitor, was recently found to inhibit P2X4 receptors in microglial cells, and reduce nerve injury-induced allodynia in rats.[1)] Therefore, chemical modification of duloxetine may lead to the development of a potent drug for treating neuropathic pain. To synthesize a variety of duloxetine derivatives in a highly efficient way, we adopted a late-stage C–H functionalization strategy. Our initial trials using conventional C–H activation methods, however, resulted in the elimination of the naphtoxy group of duloxetine by due to severe reaction conditions. Therefore, we focused on the development of a new C–H activation reaction proceeding under neutral and mild condition, and finally we achieved a selective olefination of the thienyl group of duloxetine through catalytic oxidative Mizoroki-Heck reaction using molecular oxygen as the terminal oxidant.[2)] Under the optimized reaction conditions, various alkenyl groups were introduced into duloxetine in a highly regioselective manner. The obtained products were further transformed to various duloxetine derivatives, some of which showed improved biologic activity. We further studied fundamental reactivity of the reaction against various electron-rich arenes and hetero-arenes, and applied to late-stage functionalizations of several natural and medicinal compounds to demonstrate the utility of the reaction for the construction of chemical libraries of complex molecules.

1) Yamashita, T.; Yamamoto, S.; Zhang, J.; Kometani, M.; Tomiyama, D.; Kohno, K.; Tozaki-Saitoh, H.; Inoue, K.; Tsuda, M. *PLOS ONE* **2016**, *11*(10): e0165189. doi:10.1371/ journal.pone.0165189.

2) Manuscript in preparation.