Self-assembling protein containers are promising delivery vehicles for cellular and gene therapy applications, but the ability to predict how mutations alter self-assembly and other particle properties remains a significant challenge. Here, we combine comprehensive codon mutagenesis with high-throughput sequencing to characterize the assembly-competency of all single amino acid variants of a virus-like particle. The coat protein (CP) of MS2 bacteriophage was chosen because of its potential in targeted delivery and imaging. An assembly selection revealed a high-resolution fitness landscape that challenged several conventional protein engineering assumptions. Using the same approach with additional comprehensive mutagenesis strategies and selective pressures identified several other previously-uncharacterized variants for enabling efficient chemical and post-translational modifications as well as altered stability features. For example, the wild-type CP is acid tolerant down to pH 2, but we identified a variant with a single point mutation that confers stability at neutral pH but acid-triggered disassembly. Acid sensitivity is highly desirable in targeted delivery to improve the efficiency of endosomal release. In addition to providing a blueprint of how to tune the chemical and physical properties of the MS2 CP and other structurally-related virus-like particles, these techniques can readily be applied to the systematic study of other self-assembling proteins and protein-based delivery vehicles.