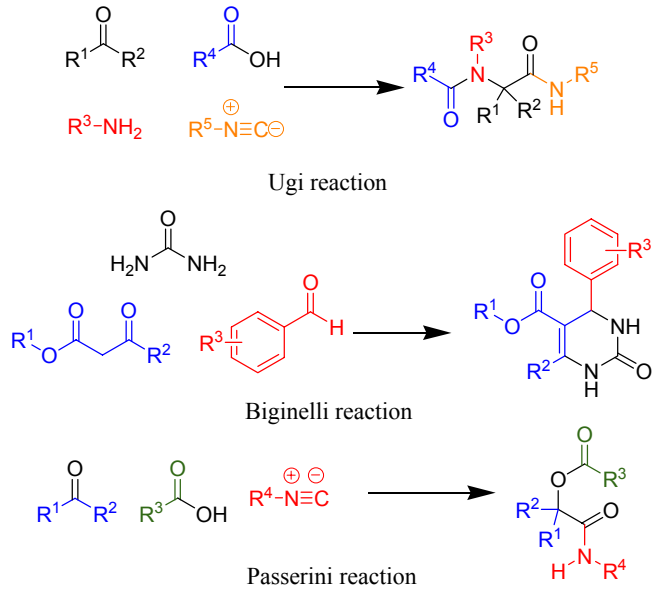

FIGURE 2.16 The Ugi reaction was discovered in 1959 by Karl Ugi, the Biginelli reaction was reported in 1891 by Pietro Biginelli, and the Passerini reaction was discovered in 1921 by Mario Passerini. These reactions have been repurposed for the preparation of large compound libraries suitable for HTS screening.

The development of high throughput screening occurred almost in parallel with high throughput chemistry, although a different set of technological advances were required. Through the 1950s, 1960s, and the 1970s, the pharmaceutical industry moved more and more towards a paradigm of screening compounds in cellular assays and isolated enzyme assays prior to animal testing in an effort to decrease costs and increase efficiency. An increasing understanding of the biochemical basis of disease provided the foundation for new biochemical assays, but the capacity to screen natural product extracts and compound collections was limited by the technology of the time. Prior to the mid-1970s and earlier 1980s, conventional methods of protein isolation and purification severely limited the amount of protein available for any given screen, thus driving up the costs. In addition, cellular assays were limited to using naturally occurring cell lines that could be grown in a reliable fashion.

The biotechnology revolution and the rise of robotics and automation, however, profoundly altered the landscape of compound screening. By the mid-1980s, major advances in biochemistry and molecular biology opened new pathways to the production of large quantities of proteins and "designer" cell lines. Technological breakthroughs, such as recombinant DNA, transfection science, polymerase chain reaction (PCR), and