Approaches such as genomics, transcriptomics, and proteomics can provide rich information about the presence and abundance of biomolecules in large populations of cells and more recently even in single cells. However, both the ensemble and single-cell versions of these techniques require the dissociation of complex structures like tissues during their experimental workflows, resulting in a loss of spatial information. Multiplexed imaging approaches capable of visualizing multiple DNA, RNA, or protein species in the same sample can provide a valuable complementary approach to the “-omics” methods, particularly in the context of tissues. We have introduced SABER—Signal Amplification by Exchange Reaction. SABER enables the multiplexed amplification of DNA and RNA fluorescent in situ hybridization (FISH) and immunofluorescence signals in fixed cells and tissues, allowing spatial patterns of gene and protein expression and chromosome organization to be mapped in their native contexts. As a proof of concept, we have performed cell-type mapping in mouse retinal tissue based on RNA and protein expression patterns and demonstrated 17-color imaging of human chromosome conformation. The SABER workflow is simple, inexpensive, and can sit on top of existing histological protocols.