The plasma membranes of eukaryotic cells are organized in an asymmetric manner for normal cellular function. At rest, polar and charged lipids are sequestered to the inner leaflet by the activity of ATP-driven pumps. Activation of a specialized class of membrane proteins – phospholipid scramblases – causes rapid collapse of this asymmetry and externalization of negatively charged phosphatidylserine molecules. As a result, extracellular signaling networks, controlling processes such as apoptosis, blood coagulation, membrane fusion and repair, are activated. The TMEM16 family of membrane proteins includes phospholipid scramblases and Cl− channels, all of which are Ca2+-dependent. Prior structural and functional analyses of the fungal TMEM16 scramblase from Nectria haematococca identified a membrane-exposed hydrophilic groove that serves as the lipid translocation pathway. In the TMEM16A channel, this pathway is sealed from the membrane, thus preventing lipid access and enabling ion permeation. However, the mechanisms underlying Ca2+-dependent gating of TMEM16 scramblases, and their effects on the surrounding lipid bilayer, remain poorly understood. Here we describe three high-resolution cryo-electron microscopy structures of a fungal scramblase from Aspergillus fumigatus, afTMEM16, reconstituted in lipid nanodiscs. Differences between the Ca2+-free and Ca2+-bound states reveal that Ca2+ binding induces a global rearrangement of the transmembrane and cytosolic regions, which causes the lipid pathway to open. Further, comparison of these structures and a third in the presence of a long-chain inhibitory lipid, together with functional experiments, reveal that scramblases cause profound remodeling of the surrounding membrane. Specifically, scramblase activation causes the bilayer to thin at the open lipid pathway and the outer leaflet to bend towards the center of the bilayer at the dimer interface. We propose a model in which trans-bilayer lipid movement is enabled by these membrane and protein rearrangements and provide a general mechanistic framework for phospholipid scrambling.