Hybridization between related species can contribute to adaptation to a novel environment, a phenomenon of particular concern for introduced species. At the same time, divergent species accumulate negative genetic interactions, which can reduce gene flow between them. These interactions are known as Dobzhansky–Muller Interactions (DMIs). To understand the balance between these two opposing processes, we simulated them together in an individual-based population genetic model. DMIs were permitted to evolve in the two divergent colonizing populations between one pair of loci by the introduction of mutations. The alleles at the loci were positively selected for in the source populations and have negative genetic interactions impacting fitness. We found that for DMIs to evolve at an appreciable frequency, strong positive selection for individual DMI alleles was necessary. When DMIs did evolve, we found that they reduced the success of hybrids at colonizing the novel environment, but only when the two-locus fitnesses were close to zero. This is the first experimental demonstration that DMIs can affect the results of hybrid colonization.