C-type lectin receptors (CLRs) that couple with the kinase Syk are major pattern recognition receptors for the activation of innate immunity and host defense. CLRs recognize fungi and other forms of microbial or sterile danger, and they induce inflammatory responses through the adaptor protein Card9. The mechanisms relaying CLR proximal signals to the core Card9 module are unknown. Here we demonstrated that protein kinase C-? (PKC?) was activated upon Dectin-1-Syk signaling, mediated phosphorylation of Card9 at Thr231, and was responsible for Card9-Bcl10 complex assembly and canonical NF-?B control. Prkcd(-/-) dendritic cells, but not those lacking PKC?, PKC?, or PKC?, were defective in innate responses to Dectin-1, Dectin-2, or Mincle stimulation. Moreover, Candida albicans-induced cytokine production was blocked in Prkcd(-/-) cells, and Prkcd(-/-) mice were highly susceptible to fungal infection. Thus, PKC? is an essential link between Syk activation and Card9 signaling for CLR-mediated innate immunity and host protection.